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Altered listening changes the way we predict the auditory environment

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Altered listening changes the way we predict the auditory environment

Pia Brinkmann

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Altered listening changes the way we predict the auditory environment

DISSERTATION

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Chapter 1

General introduction

Introduction

A current attempt to explain how the brain uses top-down predictions to sample sensory input from a dynamically changing environment is the 'hierarchical prediction machine' (Clark, 2013). This concept conceives the brain as a predictive organ, mainly occupied with reducing and correcting prediction errors. Its hierarchical structure allows for adapting at higher hierarchical levels to correct for erroneous processing at lower levels. The ultimate goal of this interplay is to continuously improve predictions by reducing prediction errors to enhance goal-directed behavior (Clark, 2013; Lee & Mumford, 2003).

Predictions occur at multiple levels of the hierarchy and can be based on different modalities. The current thesis focuses on predictions in the auditory domain. In audition, information develops over time. Other than in vision, where information can be incomplete by occlusion or a restricted field of view, temporal predictions might play a more substantial role in audition (Bendixen, SanMiguel, & Schröger, 2012). This can be assumed based on the anatomy and physiology of the hearing organ, and the propagation of sound waves. However, missing auditory information can also be restored (Miller & Licklider, 1950; Powers & Wilcox, 1977). In addition, we constantly hear something, unable to consciously close our ears as we can close our eyes. To perceive physical sound, sound waves, encompassing specific amplitudes, frequencies, and phases, travel along the classical and non-classical auditory pathways after they reach the ear and then project to higher-level temporal, parietal, and frontal cortices (Møller, 2012). While hearing may utilize attentional resources or active cognitive control, auditory predictive processing does not necessarily require attention or cognitive control (Bendixen et al., 2012; Schröger, Kotz, & SanMiguel, 2015). It can instead be an automatic process (Bendixen et al., 2012). When merely listening to auditory input over time, stimulus relations are automatically extracted, resulting in several predictions. Critically, predictions about continuous auditory input might influence how we perceive sound from simple tone sequences to music and speech in everyday life.

Imagine you take part in a race. Before the race starts, a voice might say "take your marks" or "ready, set, go", dependent on the sports discipline. In swimming competitions, we know that "take your marks" is followed by a short silence and a beep tone. Then, the swimmers shoot into the water, giving their best. Hearing this simple sound sequence may result in multiple predictions. First, we can predict *what* type of information we will hear. After the words "take your", we expect to hear "marks" and not "bananas". Second, we can predict *when* the words will occur, namely, that the time

between “take” and “your'' is similar to the time between "your" and "marks". Last, we can expect a beep tone after “marks”. We know that it will come, but not exactly when, increasing our expectation that the beep will occur when it has not yet been presented. This expectation is termed the hazard rate (Nobre & Van Ede, 2018). However, what happens when there is a technical problem, and the beep would repeat after a short time? We would likely not react as strongly to the second beep as to the first one. This can be described as gating-out or filtering of information (Schwartze, Tavano, Schröger, & Kotz, 2012). Gating is dependent on the position or timing of the beep, which means that when we hear the second beep, we react less strongly to it compared to the first beep. This example illustrates three types of auditory predictions - the ‘what’, ‘when’, and, as a special case of the latter, the ‘position’ of auditory events. Next to these types of prediction, there are other auditory phenomena that can lead to prediction errors such as omissions (Bendixen et al., 2012), where in “take … marks” the word “your” is missing. However, in the following, the focus is on the previously mentioned auditory what, when, and position predictions.

Different types of predictions facilitate auditory processing

Different types of predictability might characterize auditory sequences and lead to predictions by the listener. First, formal predictions inform the listener about ‘what’ kind of information is transmitted. An empirical exploration of formal predictions is the classical auditory ‘oddball’ paradigm, in which consecutively presented frequent standard and infrequent deviant sounds differ in their spectral information (Squires, Squires, & Hillyard, 1975). Typically, responses to a deviant sound are more pronounced relative to those to a standard stimulus (Squires et al., 1975). **Figure 1 (A)** illustrates this oddball effect as the difference between the response to a standard and a deviant tone. Second, auditory sequences can also vary in their temporal structure, leading to varying degrees of temporal predictability. Temporal predictions are predictions about ‘when’ in time an event will occur (Hughes, Desantis, & Waszak, 2013; Schwartze, Farrugia, & Kotz, 2013; Schwartze et al., 2012). Temporarily predictable sound sequences can help the listener to anticipate upcoming events and to optimize their performance (Haenschel, Vernon, Dwivedi, Gruzelier, & Baldeweg, 2005; Heideman, van Ede, & Nobre, 2018). Temporal predictability can be present in a temporally regular sequence of multiple sounds but can also emerge from repetitive grouping of sounds in a sequence, e.g., in the form of pairs. Hence, within the category of temporal predictions, one can differentiate stimulus arrangements that encompass a simple repetitive binary grouping of stimuli and corresponding position predictions. In this dissertation, it will be referred to predictions

based on the regularity of a sound sequence as temporal predictions and to predictions about the timing of a sound pair as position predictions. To further illustrate this, in **Figure 1**, temporal predictions are characterized by the difference between **(C)** and **(D)**, while position predictions are described by the difference between **(B)** and **(D)**.

In previous research, such position predictions have been explored under the umbrella term of sensory gating (SG) (Adler et al., 1982). SG is often investigated using paired tone sequences, where typically the response to the second tone is suppressed compared to the first tone (Adler et al., 1982). Initial SG research was performed in persons with schizophrenia, who were found to not show the typical suppression effect (Adler et al., 1982). Subsequently, the concept of SG was extended beyond position predictions and described as a filter mechanism that aims at filtering out irrelevant information. Filtering, or 'gating-out' sound involves selective auditory attention that may relate to predictive processes. However, separating the concepts of prediction and attention is not always straightforward, as both are related and frequently hard to distinguish (Schröger et al., 2015). In summary, it will in the following be referred to three forms of prediction (i.e., formal-, temporal-, and position predictions), where the temporal and position predictions may be considered as variants of temporal predictability.

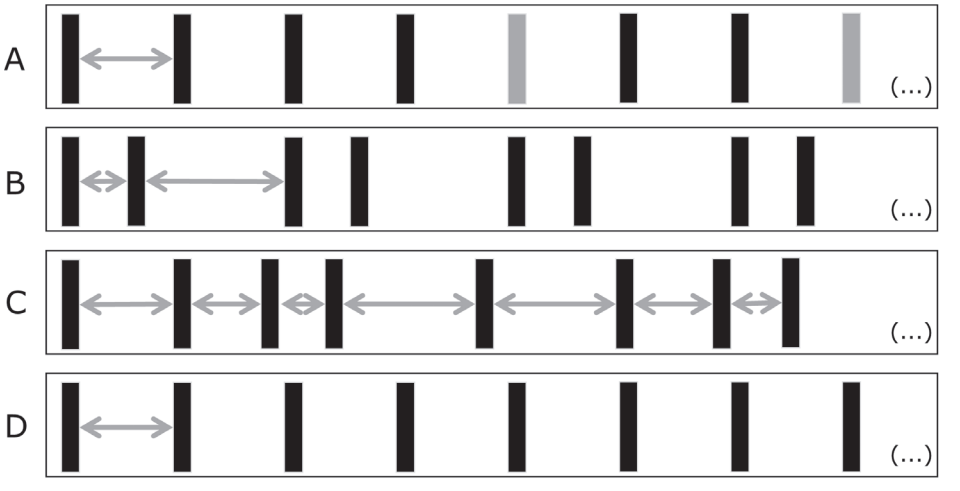

Figure 1. Schematic overview of sound sequences. An oddball sequence (A) with constant time intervals, containing frequent standard stimuli represented in black and infrequently presented deviant stimuli, depicted in gray. A sequence with paired stimuli (B) where the time interval between and within pairs is constant. Next, a sequence consisting of randomly presented stimuli (C). Last, a sequence of one repetitive stimulus with constant time intervals (D). The gray arrows indicate time intervals.

Auditory pathways

Auditory pathways contain ascending and descending connections, where information is transformed and reorganized (Møller, 2012; Oertel & Doupe, 2013). The arriving sounds travel through the outer and inner ear, until reaching the cochlea. Cochlear nerve fibers innervate the cochlear nuclei in the brain stem and project from there to the inferior colliculus in the midbrain. Originating from the inferior colliculus, two ascending pathways, the classical and the non-classical auditory pathway innervate the primary auditory cortex (PAC) and secondary auditory (Non-PAC) as well as limbic cortices (**Figure 2**) (Møller, 2012).

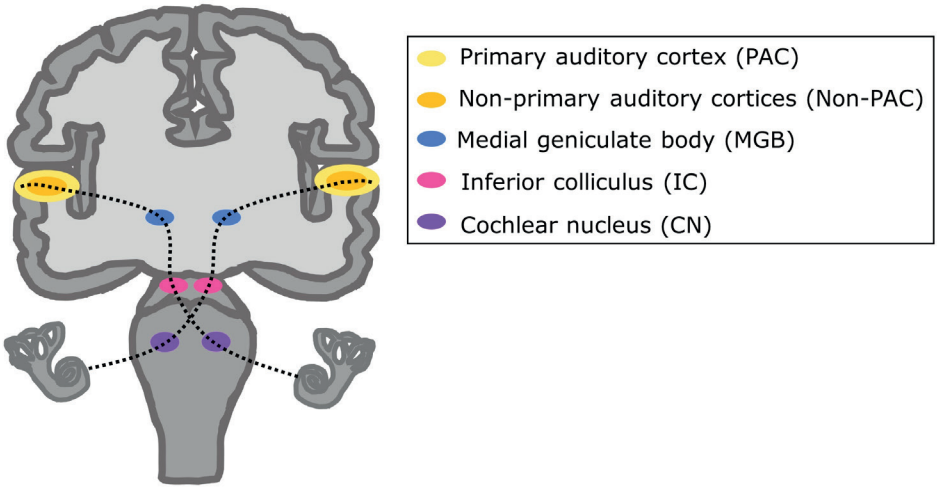

Figure 2. Schematic and simplified representation of the main nuclei of the ascending classical auditory system pathways.

The inferior colliculus divides into three distinct nuclei, the central nucleus, the dorsal nucleus, and the external nucleus. The dorsal and the external parts of the inferior nucleus are part of the non-classical pathway. The main output of the central inferior nucleus projects directly to the ventral part of the auditory thalamus, the ventral medial geniculate body (vMGB). The dorsal and medial portions of the MGB are part of the non-classical pathway. The vMGB receives direct input from the reticular nucleus in the thalamus. This structure influences the general excitability of neuronal activity in the MGB. Fibers from the vMGB terminate in the primary auditory cortex. Taken together, the classical ascending auditory pathway comprises (ipsi- and contra-lateral)

connections from the cochlear nuclei to the central nucleus of the inferior colliculus and projects to the vMGB before it reaches the primary auditory cortex. The non-classical pathway processes input beyond the auditory domain. About 10% of the neurons in the non-classical pathway have 'polysensory' properties and respond to input from auditory and somatosensory modalities (Møller, 2012; Oertel & Doupe, 2013). Signal progression along the non-classical pathway continues from the cochlear nuclei in the dorsal and external nuclei of the inferior colliculus to the dorsal and medial portions of the MGB. Non-PAC cortices receive direct projections from the dorsal and medial MGB. However, there are also connections from the dorsal and medial MGB to somatosensory association cortices and to limbic structures, such as the amygdala and subcallosal areas (Møller, 2012).

Brain correlates of (auditory) prediction

Two recent meta-analyses aimed at delineating a brain network or a set of brain areas linked to general predictive processing (Ficco et al., 2021; Siman-Tov et al., 2019). Siman-Tov et al. (2019) analyzed 39 articles assessing predictions in action perception, music, and language. They found a distributed network, encompassing cortical and subcortical structures, activated for formal predictions (i.e., what), temporal predictions (i.e., when), or spatial predictions (i.e., where). Areas involved were the inferior and middle frontal gyri, anterior insula, premotor cortex, pre-supplementary area, temporoparietal junction and subcortically, striatum, thalamus, subthalamus, and cerebellum (Siman-Tov et al., 2019). Ficco et al., (2021) analyzed 70 articles and performed analyses on prediction violation, prediction encoding, and general prediction that contained more general effects and modalities. For prediction violation, tasks were analyzed where expectations were not fulfilled, such as in mismatch or deviance detection paradigms or random conditions compared to regular ones. Prediction encoding relates to tasks where participants had to differentiate between learned and unfamiliar events or between expected and unexpected events. The general prediction condition combined the previous two conditions (Ficco et al., 2021). Results for the general prediction network differed from Siman-tov et al., (2019) and only contained cortical areas. In an additional analysis (i.e., seed-voxel correlations consensus), areas active during predictive processing were more like Siman-tov et al., (2019) and included: left inferior frontal gyrus, bilateral superior temporal gyrus, left thalamus, left hippocampus and left cerebellum (positive correlations), as well as right cerebellum, left precentral gyrus, bilateral post-central gyri and right middle occipital gyrus (negative correlations) (Ficco et al., 2021). These results suggest overlapping networks and involvement of multiple

cortical and subcortical areas, such as thalamus, cerebellum, inferior frontal gyri, or precentral gyri for predictive processing.

Models that aim at explaining timing in the brain also included cortical and subcortical areas and initially suggested that time is explicitly represented via an 'internal clock' (Buhusi & Meck, 2005; Ivry & Schlerf, 2008). One of these models is the striatal beat frequency model, which states that cortical and thalamic neurons interact with striatal spiny neurons of the basal ganglia, which act as a 'coincidence detector' that generates a 'timestamp' (Matell & Meck, 2004). The striatal beat frequency model aims at explaining interval-based auditory sequences (Buhusi & Meck, 2005; Matell & Meck, 2004). A related model attempted to explain the temporal processing of event-based auditory sequences and was labeled the cerebellar timing hypothesis (Buhusi & Meck, 2005; Ivry & Schlerf, 2008; Schwartze & Kotz, 2013). It states that the cerebellum is engaged in the processing of discrete events (Buhusi & Meck, 2005). Schwartze et al. (2012) formulated an integrative model of temporal processing in audition and speech, stating that event-based processing takes place via cerebello-thalamo-cortical connections, while longer-range intervals are encoded in the basal ganglia-thalamo-cortical system. Similarly, it was suggested that the processing of absolute, duration-based intervals recruits olivocerebellar structures and beat-based timing takes place in striato-thalamo-cortical circuits (Teki, Grube, Kumar, & Griffiths, 2011). Interestingly, they proposed that these two circuits are not independent, but interact (Teki, Grube, & Griffiths, 2012). The cortico-subcortical-cortical network of Schwartze et al. (2012), encompassing cerebellum, supplementary motor area, basal ganglia, thalamus and auditory cortex was later extended to specific temporal predictions, including a dual-pathway neural architecture model, differentiating between linear and non-linear auditory stimulus representation (Schwartze & Kotz, 2013). Schwartze et al. (2012) and (Schwartze & Kotz, 2013) underline the importance of the auditory thalamus (i.e., the MGB), as its firing modes may switch between tonic- (i.e., continuous or 'linear') and burst-mode (i.e., intermittent or 'non-linear') information coding and thereby convey different input representations to higher cortical areas (Schwartze & Kotz, 2013; Sherman & Guillery, 2006). Therefore, the thalamus with its two firing modes might differentiate between event-based representations of temporal structure and a linear representation of what events are being processed (Schwartze & Kotz, 2013).

Another approach linked to thalamocortical functioning in predictive auditory processing is the thalamocortical dysrhythmia hypothesis. It describes a condition in which abnormal firing patterns of thalamic neurons alter thalamic functioning and lead

to increased slow wave (i.e., theta, 4 – 8 Hz) oscillations (Llinás, Ribary, Jeanmonod, Kronberg, & Mitra, 1999). In addition to persistent theta oscillations emerging from the thalamus, reduction of lateral inhibition at the cortical level promotes coherent high frequency oscillations (i.e., gamma, 25 – 50 Hz) (Llinás et al., 1999). It has been suggested that the activity shift from alpha power towards increased occurrence of theta power might link to multiple symptoms observed in neurological or psychiatric conditions, such as chronic pain, Parkinson's disease, depression or tinnitus (Llinás et al., 1999). Llinás et al. (1999) further promoted that in Parkinson's, chronic pain, or tinnitus, dysrhythmia stems from impaired bottom-up functioning of the thalamus, while in epilepsy or neuropsychiatric conditions top-down influences (i.e., reduced corticothalamic input) are dominant. Thalamocortical dysrhythmia was thus associated with impaired predictions in tinnitus (De Ridder, Vanneste, Langguth, & Llinas, 2015). However, in the following, it will be discussed how altered auditory predictions may factor into tinnitus. Typical aging is then introduced in the following paragraph.

Changes in prediction in aging and tinnitus

The ability to predict auditory events changes over the lifespan (McAuley, Jones, Holub, Johnston, & Miller, 2006). Aging may therefore be conceived as a modulating factor when studying changes in predictive processes (Brown, Gruijters, & Kotz, 2022). In other words, during aging, the use of predictability might change, while pathologies such as tinnitus might be a proxy for altered or phantom perceptions. The aging process was linked to decreased inhibition and reduced cognitive control or processing speed (Braver & Barch, 2002; Salthouse, 1996; Zanto & Gazzaley, 2017). To compensate for the loss of gray matter, alternative brain regions might be recruited (Zanto & Gazzaley, 2017). Learning or acquiring new information appears more difficult in aging (Reuter-Lorenz & Park, 2010), while using and accumulating general knowledge seems to be stable or might even improve (Salthouse, 2019). More recently, it was proposed that in aging, we shift towards using already acquired knowledge, enhance our reliance on predictions (specifically when sensory reliability is decreased), and that default-executive network coupling is increased (Brown et al., 2022). When exploring auditory attention and age-related changes linked to temporal predictions, it was shown that middle-aged and older adults recruit different brain areas than younger adults (Herrmann, Maess, Henry, Obleser, & Johnsrude, 2023). More specifically, the authors found different sources of alpha power in young (i.e., superior temporal cortex and superior parietal cortex) than in old participants (i.e., superior and posterior temporal cortex and reduced power in superior parietal cortex). Moreover, in sound sequences either containing repeating

patterns or not, older adults expressed hyper-responsive reactions to sound onsets but reduced sustained neural activity in the auditory cortex when processing sound patterns (Herrmann, Maess, & Johnsrude, 2022). These results confirm differential neural signatures for temporal predictions during aging. Aging research in rats on formal predictions indicates slower adaptation to repetitive stimuli, decreased cortical firing synchrony, or decreased cortico-cortical interactions (de Villers-Sidani et al., 2010). Last, position predictions seem to not differ between older and younger adults (Gmehlin, Kreisel, Bachmann, Weisbrod, & Thomas, 2011). This suggests that for position predictions, the inhibition of redundant information seems to be preserved in aging, while processing of temporal predictions might be altered.

Another population vulnerable to changes in predictive auditory processing are persons with tinnitus. Tinnitus is frequently described as 'ringing in the ears' and is perceived as a sound in the absence of a physical sound source (Axelsson & Ringdahl, 1989; Roberts et al., 2010). Tinnitus can be described as a phantom perception that might arise from altered predictions of absent or altered auditory input (Jastreboff, 1990; Sedley, 2019; Sedley, Friston, Gander, Kumar, & Griffiths, 2016). In persons with tinnitus, structural and functional alterations were observed in auditory and non-auditory brain regions, including the dorsolateral prefrontal cortex, cingulate cortex, parietal cortex, temporoparietal junction, parahippocampus, amygdala, and insula (Elgoyhen, Langguth, De Ridder, & Vanneste, 2015). These findings led to the conceptualization of complex brain networks involved in tinnitus (Jastreboff, 1990). In animals, deafferentation at the level of the cochlea and hair cell loss was observed next to a decrease in spontaneous firing rates in the auditory nerve, and increased spontaneous firing in the cochlear nuclei (Elgoyhen et al., 2015). Moreover, increased spontaneous firing rates and neural synchrony were observed in the inferior colliculus and increased spontaneous firing rates, neuronal synchrony and tonotopic reorganization in the primary auditory cortex (Elgoyhen et al., 2015). Another animal study reported that after noise-exposure, fast responding neurons did not change their spontaneous firing rate, but expressed reduced responsiveness, while sustained and suppressed responding neurons increased their spontaneous firing activity independent of stimulus exposure (van Zwieten et al., 2021). In humans, position predictions were investigated in tinnitus and results indicated increased variability in the amount of suppression a person with tinnitus displays (Ahn et al., 2022; Campbell, Bean, & LaBrec, 2018). In animals, on the other hand, where evoked potentials in the MGB were analyzed, results indicated successful gating of formal-, temporal-, and position predictions (Zare et al., 2023). To investigate processing of formal predictions in persons with tinnitus, participants listened to standard roving

oddball sequences (Sedley, Alter, Gander, Berger, & Griffiths, 2019). Results showed no response alterations to standard and deviant stimuli in early electrophysiological responses and no effect of manipulating temporal intervals, while for later responses, differences between controls and persons with tinnitus were found (Sedley et al., 2019). Therefore, one goal of this dissertation was to review the literature on the role of the MGB in tinnitus and alterations in functional connectivity in persons with tinnitus, which resulted in the development of an alternative framework (i.e., the predictive network hypothesis) presented in **chapter 2**.

One important aspect to be considered in persons with tinnitus and in aging populations, is hearing loss. During aging, hearing abilities decrease, and in a study assessing the prevalence of hearing loss in older adults more than 45% experienced hearing loss (Cruickshanks et al., 1998). Hearing loss is a risk factor for cognitive decline, such as dementia (Thomson, Auduong, Miller, & Gurgel, 2017). The probability of developing tinnitus also increases with age (Hoffman, 2004). Moreover, it is known that tinnitus is frequently associated with hearing loss (Savastano, 2008). However, in some cases hearing loss is not detected when performing classical audiometry, such as in 'hidden hearing loss' (Liberman & Kujawa, 2017; Schaette & McAlpine, 2011; Weisz, Hartmann, Dohrmann, Schlee, & Norena, 2006). Further, more than 80% of 'normal' hearing people perceive phantom sounds when put in a soundproof room (Bo et al., 2008). Therefore, delineating the relation between hearing loss, aging, and tinnitus might be complicated.

Some authors argue that age-related hearing loss may disturb the functioning of the entire auditory system, and that tinnitus emerges due to reduced neural inhibition leading to maladaptive plasticity (Herrmann & Butler, 2021). After hearing loss, predominantly due to peripheral deafferentation, the tonotopic representation in the auditory cortex changes, similar to phantom pain. When comparing persons with hearing loss and with or without tinnitus to a control group, the tonotopic maps of persons with hearing loss were different from those of controls, but not from the hearing loss plus tinnitus group (Koops, Renken, Lanting, & van Dijk, 2020). The authors suggested that the tonotopic maps and the response amplitudes show that tinnitus might be an intermediate state between the controls and the persons with hearing loss, which might indeed be linked to reduced neural inhibition and falsely predicting auditory input (Koops et al., 2020). Yet, other authors proposed that tinnitus also occurs without hearing loss as it is also observed in children without ontological problems (Savastano, Marioni, & de Filippis, 2009). Therefore, formal predictions, which are related to the spectral information of the auditory input might be affected by the degree of hearing loss and tonotopic representation.

Electrophysiological indices of predictive auditory processing

Numerous methods have been employed in neuroscientific research to study auditory predictions. Electroencephalography (EEG) is an excellent and direct approach to measure brain activity due to its non-invasive and outstanding temporal resolution in the range of milliseconds (Berger, 1929; Gazzaniga, 2014). Before describing how the assessment of formal-, temporal-, and position predictions was implemented in the two empirical, electrophysiological experiments of this thesis, paradigms investigating auditory predictions are briefly introduced.

Paradigms exploring auditory predictions may be grouped into prediction-conforming (i.e., match) or prediction-violating (i.e., non-match) paradigms. The latter also includes omission paradigms (Bendixen et al., 2012). Under the umbrella of prediction-conforming paradigms fall paradigms such as the roving standard paradigm (Haenschel et al., 2005), adapted from Baldeweg, Klugman, Gruzelier, and Hirsch (2004) or classical sensory gating paradigms assessing position predictions (Adler et al., 1982). In this latter paradigm, two identical auditory stimuli are presented in pairs, separated by a certain temporal interval (Adler et al., 1982). Typically, the electrophysiological response to the second stimulus is filtered (indicated by a reduced response amplitude), as it is predictable based on the first tone in the tone pair (Adler et al., 1982; Cromwell, Mears, Wan, & Boutros, 2008). On the other hand, prediction-violating paradigms include the auditory oddball paradigm (Squires et al., 1975) that assesses formal predictions (e.g., Schwartze, Rothermich, Schmidt-Kassow, and Kotz (2011)). The deviant stimulus occurs with a lower probability than the standard stimulus, leading to increased electrophysiological responses (i.e., in general more negative for negative components and more positive for positive ones). The deviant tone acts as a response to an unexpected sound event, and attention is drawn to this odd stimulus, reflecting a very basic cognitive process – selective attention.

To assess temporal predictions, several experimental set-ups might be implemented. They encompass cued associations, hazard rates, simple, or more complex sequences (Nobre & Van Ede, 2018). In cued associations, a cue informs (i.e., as a warning signal) about an upcoming stimulus. Hazard rates describe a phenomenon where the probability that an event will occur is dependent on the fact that it has not occurred yet. Simple sequences can consist of isochronous recurring temporal structures, while more complex sequences can contain multiple levels of temporal predictability (Nobre & Van Ede, 2018). In general, the most pronounced differences when investigating temporal predictability might be observed when isochronous or regularly timed sequences are

contrasted with randomly timed sequences in EEG (Herrmann et al., 2022; Schwartze, Rothermich, et al., 2011).

Therefore, a second goal of this dissertation was to test formal-, temporal- and position predictions, hypothesized to facilitate goal-directed behavior, in older adults and in persons with tinnitus (Heideman et al., 2018). This was done by assessing EEG responses in oddball sequences, consisting of isochronous sequences that were compared to randomly presented standard and deviant tones (**chapter 3**). In experiment 2 (**chapter 4**), persons with tinnitus were assessed and the tones in isochronous and random sequences were grouped to form pairs, thereby allowing to also assess position predictions.

Event-related potentials

The event-related potential (ERP) of the electroencephalogram is a time-locked stimulus event response that subsumes various components. The latter are typically obtained by averaging ERPs to the same or similar stimulus events. Various ERP components can be differentiated based on their latency, polarity, and topographical distribution. The first EEG study performing a sound experiment was conducted in 1939 and by the 1960's, ERP analyses were solidly established in research (Davis, 1939; Donoghue & Voytek, 2022). Due to the widespread use of this technique, in multiple clinical populations and various cognitive phenomena, the body of ERP literature continuously grew. For example, in 2020 alone, more than 2000 ERP studies were published (Donoghue & Voytek, 2022). ERP research in audition is widely conducted, as auditory potentials evolve along a millisecond scale, allowing the assessment of several auditory ERP components.

After a sound reaches the pinna and the signal proceeds towards the brain, auditory brainstem responses occur up to 10 ms after stimulus onset (Sininger, 1993). Then mid-latency responses show between 10 and 50 ms (Pratt, 2011). Mid-latency responses begin with the last brainstem component wave V and end with the Pa component, generated in the auditory thalamus or primary auditory cortices (Kraus & Disterhoft, 1982). Long-latency potentials start at 50 ms and encompass the most pronounced auditory evoked potentials, the positive P50 and negative N100 components that occur approximately 50 to 100 ms after stimulus onset (**Figure 3,** top). The P50 and N100 are followed by other components such as the P200 or P300a/b. In the next paragraphs, it will be elaborated more on the P50 and the N100 components, which are in focus of this dissertation.

The P50 component was first investigated to assess the maturation of the auditory system (Eggermont, Ponton, Don, Waring, & Kwong, 1997). It is generated in the primary auditory cortex or Heschl's gyrus (Liegeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994). The P50 has been extensively studied with respect to SG (i.e., position predictions). Most research on the P50 focuses on SG abnormalities in schizophrenia, meaning the absence of suppression of the second tone of a tone pair (Adler et al., 1982; Patterson et al., 2008). Other populations show a similar activity pattern, such as children with autism spectrum disorder, persons with bipolar disorder, obsessive compulsive disorder, mild cognitive impairment, or Alzheimer's disease (Cheng, Chan, Liu, & Hsu, 2016; Hashimoto et al., 2008; Orekhova et al., 2008; Thomas et al., 2010). SG also changes across the lifespan. For example, in 1-4 months old infants, an enhanced suppression response was observed with increasing age (Kisley, Polk, Ross, Levisohn, & Freedman, 2003). In older adults, there is evidence for intact gating (P50), suggesting that filtering is not impaired in older participants (Gmehlin et al., 2011).

The N100 is involved in auditory signal detection (Hyde, 1997) and reflects changes in the auditory environment, such as a mismatch, a change within a sound sequence, and a fusion of acoustic elements or grouping (Pratt, 2011). The component primarily shows a fronto-central topographical scalp distribution, and the generators of the N100 are bilateral and tangential dipoles in the auditory cortices next to frontal sources (Scherg, Vajsar, & Picton, 1989; Scherg & Von Cramon, 1986). Different types of predictions can modulate N100 activity. For example, for isochronous sequences, the N100 amplitude decreases when repetitions increase (Costa-Faidella, Baldeweg, Grimm, & Escera, 2011). This phenomenon has been linked to enhanced prediction accuracy (Auksztulewicz & Friston, 2016; Winkler, Denham, & Nelken, 2009). Previous research on formal and temporal predictability found N100 amplitude differences for formal predictions expressed as more negative amplitudes for deviant stimuli (Schwartze et al., 2013). In older adults, N100 suppression for the second tone seems to be reduced (Cheng, Baillet, & Lin, 2015; Kisley, Davalos, Engleman, Guinther, & Davis, 2005). However, there is also evidence for intact N100 gating (Gmehlin et al., 2011). Therefore, filtering of redundant information does not seem impaired in older participants (Gmehlin et al., 2011), while others suggest impaired SG in older adults (Cheng et al., 2015; Kisley et al., 2005).

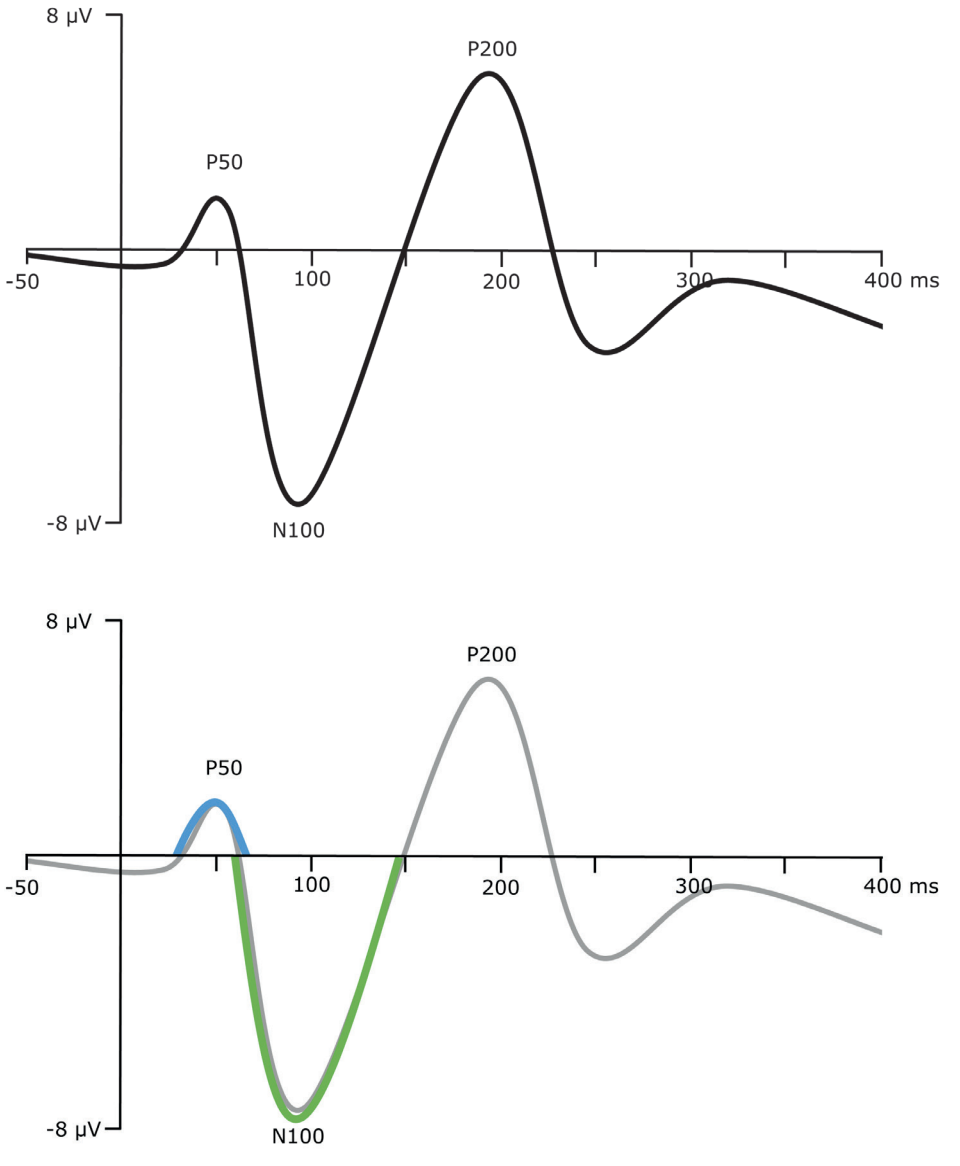

Figure 3. Top: Illustration of auditory long-latency evoked potentials with the labels of some ERP components. Bottom: Example of how a temporal principal component analysis might extract the underlying components for the P50 and the N100.

Temporal spatial principal component ERP analysis

ERPs consist of summed potentials of multiple neuronal populations. To disentangle a possible overlap of evoked responses and to delineate latent ERPs, temporal-spatial principal component analysis (tsPCA) can be applied (Dien, 1998; Foti, Hajcak, & Dien,

2009). Principal component analysis (PCA) is a data-driven process to reduce the number of dimensions in a big dataset, while trying to keep the maximum amount of information. First attempts to extract linear combinations of data points across temporal and spatial dimensions started already in 1998 and are now well established in ERP research (Dien, 1998, 2010a). A frequent approach to perform tsPCA encompasses a two-step procedure, first in the temporal domain, with a temporal PCA using an oblique promax rotation (Hendrickson & White, 1964), followed by an independent component analysis (ICA), using an informax rotation in the spatial domain (Bell & Sejnowski, 1995; Delorme & Makeig, 2004; Dien, 2010b). Oblique factor rotations allow factors to be correlated, which is especially useful when time points are used as input variables, which is the case for step one in tsPCAs. In step two, the infomax rotation aims at maximizing statistical independence between factors (Dien, 2010b; Dien, Khoe, & Mangun, 2007). Typical analyses use all time points of averaged trials per participant, for each electrode, and events. After performing this analysis, it is possible to inspect the temporal distributions (i.e., including peak latencies) of the temporal components generated during step one and to check the distributions of the regions of interest (ROIs) extracted in step two. How two temporal components might extract underlying ERP activity and consequently be selected by the researcher is illustrated at the bottom of **Figure 3**, (i.e., the focus is on the P50 and N100 for this thesis). After performing step two, a combination of temporal-spatial factors can be selected that represents the ERP of interest most accurately. This approach is widely used and applied in multiple areas of EEG research, such as emotion processing (Foti et al., 2009), memory retrieval (Haese & Czernochowski, 2022), and investigations in clinical populations such as persons with obsessive-compulsive disorder (Klawohn, Riesel, Grützmann, Kathmann, & Endrass, 2014). This method was used in the data analysis presented in **chapter 4**.

Overview

This thesis consists of one review paper and two empirical EEG experiments, investigating predictive auditory processing. **Chapter 2** presents the review article and discusses how the auditory thalamus, the medial geniculate body (MGB), might be involved in monitoring temporal predictions in persons with tinnitus and, to this end, presents a predictive network hypothesis. This hypothesis was informed by the dual-pathway architecture for temporal processing (Schwartze & Kotz, 2013) and extended it to a pathological population, represented by persons experiencing tinnitus, while reflecting on cortical connections and functions of the MGB. **Chapter 3** presents the first empirical chapter and reports results on how younger and older adults differ in their use of formal and temporal predictions while processing auditory tone sequences.

The paradigm comprised two auditory oddball sequences, where the first sequence was timed regularly (i.e., isochronous) and the second randomly, that is the intervals between tones varied (see also Schwartze, Rothermich, et al. (2011)). For the study presented in **chapter 4**, the previously applied paradigm was extended to not only assess formal and temporal predictions, but also position predictions. This was achieved by adapting the timing between two consecutive sounds and implementing it in two oddball sequences consisting of paired stimuli. This means that the pair timing (i.e., the timing between tones in a pair) was shorter than the inter-pair timing (i.e., the timing between pairs). Through this adaptation, this second empirical chapter aimed to disentangle formal predictions from temporal- and position predictions, and to compare all predictive processes in persons with or without tinnitus. Finally, **chapter 5** provides a general discussion of the results. It elaborates on similarities and differences between the preceding chapters, aiming to explain the differences. Thalamocortical dysrhythmia in tinnitus is discussed in addition to the concept of sensory gating and phantom perception, thereby providing an outlook and conclusion.


2

Chapter 2

Auditory thalamus dysfunction and pathophysiology in tinnitus: A predictive network hypothesis

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Abstract

Tinnitus is the perception of a 'ringing' sound without an acoustic source. It is generally accepted that tinnitus develops after peripheral hearing loss and is associated with altered auditory processing. The thalamus is a crucial relay in the underlying pathways that actively shapes processing of auditory signals before the respective information reaches the cerebral cortex. Here, we review animal and human evidence to define thalamic function in tinnitus. Overall increased spontaneous firing patterns and altered coherence between the thalamic medial geniculate body (MGB) and auditory cortices is observed in animal models of tinnitus. It is likely that the functional connectivity between the MGB and primary and secondary auditory cortices is reduced in humans. Conversely, there are indications for increased connectivity between the MGB and several areas in the cingulate cortex and posterior cerebellar regions, as well as variability in connectivity between the MGB and frontal areas regarding laterality and orientation in the inferior, medial and superior frontal gyrus. We suggest that these changes affect adaptive sensory gating of temporal and spectral sound features along the auditory pathway, reflecting dysfunction in an extensive thalamo-cortical network implicated in predictive temporal adaptation to the auditory environment. Modulation of temporal characteristics of input signals might hence factor into a *thalamo-cortical dysrhythmia* profile of tinnitus but could ultimately also establish new directions for treatment options for persons with tinnitus.

Introduction

Tinnitus is frequently described as hearing a sound without an external source or as a ringing in the ears (Baguley, McFerran, & Hall, 2013). The prevalence of tinnitus ranges from 10-15% in the general population, and in 1-2% it severely interferes with the affected person's daily life (Langguth, Kreuzer, Kleinjung, & De Ridder, 2013; McCormack, Edmondson-Jones, Somerset, & Hall, 2016; Schlee et al., 2017). Severe forms of tinnitus exert a particular negative impact on the quality of life, with symptoms of depression, anxiety, sleep disturbances, concentration difficulties, or reduced cognitive efficiency (Hallam, McKenna, & Shurlock, 2004; Langguth, 2011). Consequently, tinnitus has direct societal impact, as reflected in high healthcare costs and loss of productivity (Maes, Cima, Vlaeyen, Anteunis, & Joore, 2013). Currently, there is no curative evidence-based therapy for tinnitus, i.e., although drug targets, cognitive, behavioral, and neuromodulative interventions have been put forward, there is a lack of randomized controlled trials confirming effective tinnitus treatment (Kleinjung & Langguth, 2020).

Over the past two decades, general interest in tinnitus has rapidly grown as part and parcel of new hypotheses about tinnitus pathophysiology (Møller, Salvi, De Ridder, Kleinjung, & Vanneste, 2015; Roberts & Salvi, 2019). Reflecting parallel advances in neuroimaging methodology, the general focus shifted from otology to neuronal correlates of tinnitus (Langguth et al., 2013). Although there is no strong consensus, it is generally assumed that hearing loss precedes the development of tinnitus. Consequently, changes along the classical and non-classical auditory pathway, expressed in alterations of spontaneous firing activities, neural synchronization, or tonotopic organization are possible key elements of tinnitus pathogenesis (Elgoyhen et al., 2015).

The classical ascending auditory pathway includes projections to mainly primary auditory regions, while non-classical auditory pathways have been described as extralemniscal, diffuse, or polysensory pathways that involve connections to non-primary auditory areas (**Figure 1**) (Aitkin, 1986; Graybiel, 1972; Møller, 2012). Next to neural correlates of tinnitus, current theories suggest maladaptive gating, increased central gain or altered neural thalamo-cortical coherence as factors underlying the development of tinnitus (De Ridder et al., 2015; Llinás et al., 1999; Norena, 2011; Rauschecker, Leaver, & Mühlau, 2010). However, although the auditory thalamus, and in particular the medial geniculate body (MGB), is a mandatory relay station along the auditory pathway, its contribution to tinnitus pathology is often disregarded.

The MGB is part of the classical and non-classical auditory pathway, mediating the thalamo-cortical network involved in tinnitus. It actively shapes information processing between subcortical and cortical areas (Bartlett, 2013; De Ridder et al., 2015; Llinás et

al., 1999). Animal research provides first indications of successful tinnitus treatment by invasively stimulating the MGB in rats (van Zwieten, Janssen, et al., 2019). The MGB should hence not only be considered a major gateway station for auditory signals transmitted to the cerebral cortex, but also as a crucial component in developing a better understanding of tinnitus pathology (Leaver et al., 2011; Møller, 2003). Taking this perspective and starting with a review of thalamic contributions to auditory processing, we formulate a hypothesis of thalamic functioning in tinnitus pathology from a comparative perspective, integrating animal and human evidence. We propose that changes in thalamic functioning affect sensory gating at the level of the MGB, suggesting a dedicated timing and temporal prediction mechanism as an independent source of information and a potential tool for modulating the experience of tinnitus.

Functional neuroanatomy of the medial geniculate body of the thalamus

To improve understanding of tinnitus and the role of the auditory thalamus in tinnitus pathophysiology, it is necessary to first consider the functional anatomy of the MGB. In general, the auditory pathway contains ascending and descending connections to auditory cortices and along its way, information is transformed and reorganized (Møller, 2011; Oertel & Doupe, 2013). Input travels through the ear, the cochlea (**Figure 1**), the cochlear nuclei (CN) and the inferior colliculus (IC) before reaching the MGB (Oertel & Doupe, 2013). .

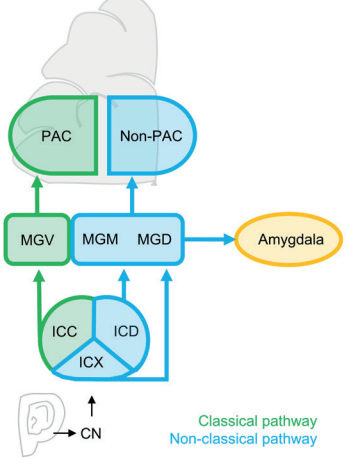

Figure 1. Schematic and simplified representation of the classical and non-classical ascending auditory pathway. Ascending auditory signal travels from the ears to primary and secondary auditory cortices, while taking two different pathways. PAC, Primary auditory cortex, Non-PAC, Non-primary auditory cortices, CN, Cochlear nucleus, ICC, Central inferior colliculus, ICD, Dorsal inferior colliculus, ICX, External inferior colliculus, MGB, Medial geniculate body, MGD, dorsal MGB, MGM, medial MGB, MGV, ventral MGB.

Originating from the IC, two ascending pathways, the classical and the non-classical auditory pathway innervate the MGB, primary (PAC) and non-primary auditory cortices (non-PAC), as well as limbic regions (Møller, 2002; Pickles, 2015). The IC can be divided into three distinct nuclei, the central part of the IC (ICC), the dorsal cortex of the IC (ICD), and the external nucleus of the IC (ICX). In the classical pathway, the ICC provides the main input to the ventral MGB (MGV; see **Table 1** for an overview).

Table 1. **Overview of MGB subdivisions and their functionality**.

	Ventral MGB	**Medial MGB**	**Dorsal MGB**
Primary role in functional neuroanatomy	Auditory relay	Multisensory relay	Multisensory relay
Classical/Non-classical auditory pathway	Classical	Non-classical	Non-classical
Input	Ipsilateral central nucleus of the IC	External IC, dorsal IC, central IC, lateral tegmentum, spinal cord, superior colliculus	Dorsal IC, tegmentum, sagulum, somatosensory system
Output	Ipsilateral primary auditory cortex (PAC)	Primary and secondary auditory cortices (PAC, Non-PAC), lateral nucleus of the amygdala, non-auditory areas, striatum	Secondary auditory cortices (Non-PAC, i.e. belt areas), lateral nucleus of the amygdala, non-auditory areas
Responses to sound	Sharp tuning curves, single-peaked, short tone latency, closely connected to the PAC	Heterogeneous tuning curves, spatial selectivity, s tone latency, fire at stimulus onset, associative learning responses (i.e. fear conditioning)	Wide, multipeaked tuning curves, short and long tone latency, sharp tuning curves, habituation and stimulus adaptation
Tonotopic organization	Yes	Yes (less than ventral MGB)	No
Tonotopic map	Low-to-high (ventro-lateral-dorsomedial)	NA	NA

Abbreviations: PAC, Primary auditory cortex, Non-PAC, Non-primary auditory cortex, IC, Inferior colliculus, MGB, Medial geniculate body.

The MGV forms the “core” subdivision of the MGB. The MGV has a pronounced tonotopic organization, narrow tone frequency tuning, and exclusively responds to auditory input (Aitkin & Webster, 1972; Bartlett, 2013; Hackett, Barkat, O'Brien, Hensch, & Polley, 2011). Fibers from the MGV primarily innervate the primary auditory cortex (Bartlett, 2013).

The non-classical pathway processes input beyond the auditory domain and innervates limbic regions, such as the amygdala, next to primary and secondary auditory cortices (Bartlett, 2013; Møller, 2002). The ICD and the ICX provide input to the medial and dorsal subdivisions of the MGB in the non-classical pathway. The dorsal subdivision of

the MGB (MGD) is not tonotopically organized (Bartlett, 2013) and projects to the Non-PAC, the lateral nucleus of the amygdala and non-auditory areas (Bartlett, 2013). The medial subdivision of the MGB (MGM) is the most heterogeneous part of the MGB. The tonotopic organization of the MGM is not as pronounced as in the MGV, tone frequency tuning is heterogeneous and neurons in the MGM respond not only to auditory, but also to visual and somatosensory input (Bartlett, 2013; Hackett et al., 2011; Rouiller et al., 1989). Projections from the MGM terminate in primary and non-primary auditory cortices as well as the amygdala (Aitkin, 1986; Bartlett, 2013; Møller, 2002). Moreover, all MGB subdivisions receive input from the reticular nucleus in the thalamus (TRN), which influences general excitability of neuronal activity in the MGB (Bartlett, 2013; Møller, 2002).

Consequently, classical and non-classical ascending auditory pathways contribute differently to the processing of auditory stimuli in the MGB and most likely to tinnitus pathophysiology. Due to the different input and output structures, the three subdivisions of the MGB may form three separate and parallel pathways to higher cortical auditory areas (Pickles, 2015; Winer, Miller, Lee, & Schreiner, 2005).

Tonotopic map and sound level tuning in the MGB

As described above, the MGB is divided into different parts, the MGD, MGM and MGV. These parts have different neurophysiological properties and respond differently to external auditory stimuli. Frequency maps have been created in animal models by means of electrophysiological studies. Frequency tuning in the MGB is sharpest in the MGV in awake marmoset primates (Bartlett, Sadagopan, & Wang, 2011). Similar results were obtained in rats (Bordi & LeDoux, 1994). Comparable to the MGV, neurons in the MGM have also been shown to respond in a narrow fashion in the anesthetized rat (Anderson & Linden, 2011). An intermediate level of frequency tuning has been described for the MGD (Bartlett, 2013). However, results are not consistent fast habituation to repeated stimuli using isointensity tones in the MGD are described in Bordi and LeDoux (1994). The picture is even more complex as recent evidence suggests more variable tonotopic maps for neurons with multi-peaked frequency tuning curves (Gaucher et al., 2019).

Sound level tuning on the other hand, is monotonic, i.e. the sound intensity changes, while the frequency remains stable. Neurons exhibiting either a progressive increase or a progressive decrease in firing rates when intensity changes can be classified as monotonic. Non-monotonic responses are observed when firing rates increase with increasing tone intensity until a plateau is reached, after which firing rates decrease.

Rouiller, de Ribaupierre, Morel, and de Ribaupierre (1983) investigated sound level tuning in the MGB in anesthetized cats and found that most units exhibited non-monotonic responses.

Animal studies investigating the MGB predominantly rely on invasive techniques whereas in human studies non-invasive methods are predominant due to self-evident ethical reasons. This makes the identification and subsequent manipulations of the small (i.e., 5x4x5mm, Winer et al., 1984) and densely clustered MGB nuclei intrinsically difficult. Technological advances such as ultra-high field functional neuroimaging (i.e. 7T) allow creating precise tonotopic maps of the human MGB (Berlot et al., 2020; Mihai, Moerel, et al., 2019; Moerel, De Martino, Ugurbil, Yacoub, & Formisano, 2015). These functional magnetic resonance imaging (fMRI) techniques allow high spatial resolution imaging but depend on slow changes in blood oxygenation. Thus the signal depends on the vascular morphology of the relatively small MGB (Moerel et al., 2015). In humans, a low-to-high tonotopic map has been identified in the MGV in a ventrolateral-dorsomedial direction (Moerel et al., 2015). Moerel et al. (2015) further observed another, dorsomedial area with a preference for low frequency stimuli, located outside the MGV. Berlot et al. (2020) investigated the MGB tonotopy in persons with tinnitus and healthy controls, confirming a low-high-low frequency preference in the sagittal plane, comparable between groups. Tonotopic organization of the MGV and of the pars lateralis (PL) in the MGB in anesthetized cats has been found to also range from low-to-high in a latero-medial gradient (Aitkin & Webster, 1972; Morel, Rouiller, de Ribaupierre, & de Ribaupierre, 1987). Thus, mounting evidence supports a roughly similar low-to-high tonotopic organization in animals and humans in the MGV, validating the comparative usage of animal models.

Representation of complex sounds

It is likely that artificially created sine tones do not entirely capture the functioning of the MGB when it perceives more complex auditory stimuli, such as vocalizations. In awake guinea pigs, the MGB has been shown to respond to amplitude modulated (AM) and frequency modulated (FM) sine tones as well as to natural calls (Creutzfeldt, Hellweg, & Schreiner, 1980). Interestingly, the MGB responded to natural calls of the same and of other species, and its response was depicted in more detail in the MGB than in cortical cells, meaning that MGB units could differentiate between high modulation frequencies, while cortical cells could not (Creutzfeldt et al., 1980).

Discrimination of speech-like contrasts seems to occur at the level of the MGB, as observed in mismatch responses in the caudo-medial MGB of guinea pigs (Kraus et al.,

1994). Cai, Richardson, and Caspary (2016) investigated whether young, old, awake, or anesthetized rats differentially process complex auditory stimuli in the MGB. They found that MGB cells in the old awake rat preferred regular predictable, vocalization-like signals, especially when increasing the difficulty in modulation frequency (Cai et al., 2016). In young rats, however, randomly presented modulated sequences were preferred (Cai et al., 2016). This suggests that with increasing age, top-down processes may enhance the processing of expected stimuli with the same formal structure at the level of the MGB. Accordingly, previous research shows that the MGB is not only tonotopically organized, but that it is closely involved in the representation of complex vocalizations across species and that its functioning may change across the life span (i.e. preferring predictable stimuli) (Amin, Gill, & Theunissen, 2010; Cai et al., 2016; Huetz, Philibert, & Edeline, 2009; Kraus et al., 1994).

Human research specifically targeting MGB activity in response to human vocalization and speech is rare (Mihai, Moerel, et al., 2019; Mihai, Tschentscher, & von Kriegstein, 2019b). The MGB is active irrespective of content or loudness manipulations of speech sounds (von Kriegstein, Patterson, & Griffiths, 2008). Mihai, Moerel, et al. (2019) assessed speech recognition abilities in the core subdivision of the auditory thalamus (i.e., MGV) and found behaviorally-relevant task dependent fMRI modulation of the left MGV. Furthermore, left MGV was found to be increasingly activated when participants had to recognize speech in noise compared to intelligible speech (Mihai, Tschentscher, & Von Kriegstein, 2019a). Previously, the ventral intermediate nucleus (VIM) has been reported to respond to syntactic and semantic components in spoken language (Wahl et al., 2008). In addition, it has been proposed that the thalamus contributes to speech processing via its differential encoding of temporal and spectro-temporal information (Kotz & Schwartze, 2010). Taken together, evidence across several species indicates that the MGB dynamically shapes simple tones and complex vocalizations before auditory sensations reach the cerebral cortex.

Information processing in the MGB – intrinsic cell properties

To gain better understanding of information processing in the auditory thalamus and how these processes transform auditory information before it reaches the cortex, it is necessary to focus on specific electrophysiological properties of MGB neurons. Thalamic neurons respond to incoming information in either a burst or a tonic mode (Sherman & Guillery, 2006). Thus, questions arise as to how the two firing modes (i.e. burst and tonic mode) emerge and how they shape auditory information processing.

Next to classical action potentials (i.e., single-spikes), low threshold spikes (LTS) are important voltage dependent conductance mechanisms for thalamic relay cells (Jahnsen & Llinas, 1984b; Sherman & Guillery, 2006). A LTS involves the membrane depolarization of T-type voltage-gated calcium channels (Jahnsen & Llinas, 1984a, 1984b), while classical action potentials are provoked by the opening of sodium (Na^+) channels. The threshold to elicit a LTS is approximately 10 mV lower (i.e., more hyperpolarized) than for classical action potentials (Hu, 1995; Jahnsen & Llinas, 1984b; McCormick, Pape, & Williamson, 1991). In addition to the fact that T-type calcium channels act on more hyperpolarized membrane potentials, than sodium channels, T-type calcium channels are slower and need approximately 100 ms to switch between states of inactivation (Sherman & Guillery, 2006).

Of specific interest for subsequent information processing in the MGB are the two different firing modes in response to LTSs. The state of the T-type calcium channels, determines the respective firing mode of the thalamic neurons (Ramcharan, Gnadt, & Sherman, 2000). Irrespective of the neuron type, thalamic neurons have been found to respond in either a tonic or a burst mode and also switch between these modes (Jahnsen & Llinas, 1984b; McCormick et al., 1991; Sherman, 2001; Sherman & Guillery, 2006). The tonic mode has been described as preserving input linearity, whereas the burst mode acts as a 'wake-up call' to cortical targets (Ramcharan et al., 2000; Sherman, 1996). Rhythmic burst firing has been primarily observed during sleep, potentially indicating reduced transmission of sensory information to the cortex (Domich, Oakson, & Steriade, 1986; Sherman & Guillery, 2006). However, it has been shown that burst firing is not limited to sleep and can be recorded from the thalamus of awake behaving macaque monkeys (Ramcharan et al., 2000). Information processing in burst mode has been suggested to be less detailed and less noisy, but also more efficient, as only infrequent 'wake-up calls' are processed (Sherman & Guillery, 2006). Information processing in the tonic mode, however, maintains a more detailed representation of an input signal (i.e., more linearity).

When T-type channels are inactivated by membrane depolarization, the tonic mode is elicited (Ramcharan et al., 2000). To elicit burst firing, T-type calcium channels are activated from a hyperpolarized condition (Ramcharan et al., 2000). In mice, it was shown that switching between burst and tonic firing in MGV neurons partly underlies paired-pulse depression in thalamo-cortical neurons (Bayazitov, Westmoreland, & Zakharenko, 2013). Bayazitov et al. (2013) employed an auditory paired-pulse paradigm (i.e., intra-pair-interval = 100 -1000 ms, inter-pair interval = 500 -10000 ms) and found

that thalamic neurons responded to the first tone of the pair with a burst, followed by a single-spike action potential. Furthermore, it was found that the point of switching between the burst firing single-spike pattern to a single-spike single-spike pattern in response to a stimulus pair occurs around an inter-pair-interval of 1000ms, when applying intra-pair-intervals of 200-1000ms (Bayazitov et al., 2013). These results indicate temporal sensitivity when switching between the tonic and the burst firing mode. A similar hypothesis has previously been formulated by Bartlett (2013), stating that in speech, where fast-changing temporal features are common, burst firing may encode the rhythmic dynamic of syllabic on- and offsets, while tonic firing may help discriminating between finer, more faint auditory signals. In addition, it has been suggested that burst mode patterns are more frequently encountered in MGD neurons and single-spike firing predominantly in MGV (Hu, 1995), a pattern that has not been confirmed by Bartlett and Smith (1999). Thalamic cells thus fire in a burst or a tonic mode, which map onto non-linear and linear information processing, respectively. However, it is unclear how the different firing modes and spiking patterns may relate to tinnitus pathology.

The MGB in tinnitus pathology

Animal models of tinnitus are frequently employed to systematically investigate the pathophysiology of tinnitus and the changes it causes along the auditory pathway, including the MGB. These models can be broadly divided into interrogative models and reflexive models (Brozoski & Bauer, 2016; Galazyuk & Brozoski, 2020). Interrogative models evaluate voluntary behavior (i.e., performing an action to obtain food when hearing a sound), while reflexive models evaluate involuntary behavioral responses to the acoustic startle reflex (Brozoski & Bauer, 2016; Galazyuk & Brozoski, 2020). Across species, the most frequently employed reflexive model uses the gap-prepulse inhibition of the acoustic startle (GPIAS) to determine the presence and course of tinnitus pathology (Galazyuk & Hebert, 2015; Turner et al., 2006). To induce tinnitus, animals are either administered high doses of sodium salicylate (Su et al., 2012; Yang et al., 2007) or exposed to loud sound (Brozoski & Bauer, 2016). In the latter case, animals under anesthesia are unilaterally exposed to loud broad-band noise while the contralateral ear is plugged to prevent hearing loss. In the GPIAS paradigm, acoustic startle responses are reduced, when a silent gap (e.g., 50 ms) is inserted before the startle sound (Smit et al., 2016). However, when a sound matching the tinnitus frequency is played and a silent gap is presented, the gap will not be perceived by the animal experiencing tinnitus, because it has been filled-in by the tinnitus frequency (Turner et al., 2006). Thus, animals experiencing tinnitus show

increased startle responses in comparison to unexposed controls (Turner et al., 2006; Yang et al., 2007). Advantages of the GPIAS model are that it is relatively fast to administer, does not require training, and motivational states (i.e., frequently managed via diet restrictions) play a minor role (Brozoski & Bauer, 2016). One of the disadvantages is habituation, i.e., when repeated, unconditioned reflexes diminish in amplitude (Lobarinas, Hayes, & Allman, 2013; Longenecker & Galazyuk, 2011). This issue was addressed by administering fewer trials and by randomly varying the inter-stimulus interval (van Zwieten, Jahanshahi, et al., 2019; van Zwieten, Janssen, et al., 2019). Based on the assumption that tinnitus pathogenesis relies on malfunctioning of a vast network of primary auditory and non-auditory structures (Llinás et al., 1999; Rauschecker et al., 2010), it has also been criticized that the GPIAS model does not take hyperacusis and emotional factors such as stress into account (Brozoski & Bauer, 2016; Kleinjung & Langguth, 2020). Thus, evaluating animal studies investigating MGB functioning in tinnitus pathology requires close monitoring of the paradigm choice, because even if motivational states do play a minor role in the GPIAS model, stress might still influence an animal's performance.

Animal studies investigating the MGB in tinnitus

Several studies investigated MGB changes in tinnitus animal models (**Table 2.**).

However, due to heterogeneous methodology and the overall limited number of studies, it is difficult to identify generalizable result patterns. When focusing on changes related to neurotransmitters, decreased GABA has been found in the MGB in rat models of tinnitus (Brozoski & Odintsov, 2012; Llano, Turner, & Caspary, 2012). However, contradicting evidence exists (Sametsky, Turner, Larsen, Ling, & Caspary, 2015). Administering high doses of sodium salicylate decreased the excitability of neurons in the MGB, leading to increased hyperpolarization of resting state potentials (Su et al., 2012; Wang et al., 2016). Another approach to assess alterations in the MGB in animals experiencing tinnitus is to investigate firing patterns, *in vitro* or *in vivo* in either anesthetized or awake animals. *In vitro*, both healthy control animals and rats with behavioral evidence of tinnitus, displayed burst firing after a current injection to the soma (Sametsky et al., 2015). Animals with tinnitus had an increased number of spikes per burst in comparison to controls and increased tonic $GABA_A$ currents. This suggests a shift towards increased tonic inhibition, which may result in abnormal bursting activity in the MGB, in turn leading to increased output from the MGB to higher auditory cortices (Sametsky et al., 2015). Moreover, Sametsky et al. (2015) investigated whether changes in LTS responses could be associated to the increase of spikes per burst in rats with tinnitus.

Table 2. Animal studies investigating the MGB in tinnitus.

Study	Subjects	Tinnitus induction	Tinnitus assessment	Paradigm	Method	Activity
Brozoski et al. 2012	10 Ctrl, 10 Tin	Unilateral NT (1h, band limited noise)	Interrogative model	in vitro - Spectroscopy	Proton magnetic resonance spectroscopy	Decrease GABA and Glu in contralateral MGB
Su et al. 2012	6 Tin	Sodium salicylate	Reflexive model (GPIAS)	in vitro - Single cell	Whole-cell patch-clamp	Decreased synaptic transmission (Hyperpolarization resting membrane potential; decreased firing rates)
Kalappa et al. 2014	9 Ctrl, 6 Tin	Unilateral NT(1h, octave band noise)	Reflexive model (GPIAS)	in vivo (awake) - Single cell	Tetrode microdrives	Increased spontaneous firing in Tin, mean bursts per minute, mean spikes per burst and mean burst duration
Sametsky et al. 2015	10 Ctrl, 14 Tin, 4 non-Tin	Unilateral NT (1h, octave band noise)	Reflexive model (PPI)	in vitro - Single cell	Whole-cell patch-clamp	Increase in nr. of spikes per burst
Vianney-Rodrigues et al. 2019	10 Tin	Sodium salicylate	none	in vivo (anesthetized) - LFP	Microelectrode arrays	Decrease theta, alpha, beta, increased coherence in gamma
Barry et al. 2019	12 Ctrl, 16 Tin	Unilateral NT (2h, pure tone)	Reflexive model (GPIAS, PPI)[a]	in vivo (anesthetized) - Single cell	Microelectrodes	No differences for spontaneous firing rates between groups, increased bursting patterns in Tin, decreased percentages of spikes per burst in Tin
Van Zwieten et al. 2021	5 Ctrl, 9 Tin	Unilateral NT (1.5h octave band noise)	Reflexive model (GPIAS)[b]	in vivo (anesthetized) – Single cell & LFP	Microelectrode & Bipolar electrode	Decrease in fast responding neurons, increase in non-responsive neurons, increased spontaneous firing in neurons of sustained and suppressed type, fast responding neurons did not change the spontaneous firing rate, in both groups: DBS suppressed thalamocortical synchronization in beta and gamma bands

[a] Tinnitus was assessed using the GPIAS and the PPI model on a subgroup $n = 9$ from the $n = 16$ Tin rats.
[b] The set-up did not allow valid discrimination between non-Tin and Tin animals.
Abbreviations: Ctrl, Control animals, GABA, Gamma-aminobutyric acid, GPIAS, Gap-prepulse inhibition of the acoustic startle, Glu, Glutamate, LFP, Local field potential, non-Tin, Noise exposure but no tinnitus, NT, Noise trauma, PPI, Prepulse inhibition, Tin, Animals experiencing tinnitus.

The authors found no differences between tinnitus and control animals in amplitude or area of LTS for bursts elicited by injecting a hyperpolarizing current. Thus, suggesting that multiple and additional mechanisms might play a role in the excitability of MGB neurons. Another study observed reduced numbers of neurons exhibiting burst activity patterns, decreased spikes per burst and bursts per minute in anesthetized rats who were administered an acoustic noise trauma, irrespective of tinnitus presence (Barry, Robertson, & Mulders, 2019). Another study investigating the MGB in anesthetized rats with and without noise exposure classified four response types (i.e., fast, sustained, suppressed and no response) (van Zwieten et al., 2021). It was found that noise exposure resulted in an overall decrease of fast responding neurons, while non-responsive increased (van Zwieten et al., 2021). In addition, spontaneous firing rates increased in sustained and suppressed neurons, while this was not the case for fast responding neurons. Acquired LFPs suggest suppressed thalamocortical synchronization in the beta and gamma bands, independent of noise trauma (van Zwieten et al., 2021).

Oscillatory coherence between the MGB and the primary auditory cortex has been investigated using local field potentials (LFP) in anesthetized rats, while tinnitus was induced by sodium salicylate (Vianney-Rodrigues, Auerbach, & Salvi, 2019). Results indicate that sodium salicylate decreased theta, alpha, and beta oscillations in the MGB. Decreased coherence (i.e., the strength of a correlation between two signals as a function of frequency) between theta and alpha oscillations was further observed, while gamma coherence was increased between pairs of electrodes positioned in the MGB and PAC (Vianney-Rodrigues et al., 2019). Interestingly, when assessing the coherence (i.e., synchrony) between the MGB and PAC, sodium salicylate decreased coherence measures in the beta, alpha, and theta bands and again, enhanced coherence for the gamma band (Vianney-Rodrigues et al., 2019). Enhanced gamma coherence relates to previous research, as gamma band activity was suggested to be a direct neural correlate of tinnitus, influencing thalamo-cortical networks (Schlee, Hartmann, Langguth, & Weisz, 2009; Sedley et al., 2012; van der Loo et al., 2009).

In awake rats, Kalappa et al. (2014) found similar results as Sametsky et al. (2015), confirming increased number of bursts per minute, increased mean burst duration and mean spikes in a burst. Kalappa et al. (2014) showed increased spontaneous firing in the MGD, MGM, and the MGV in a rat model of tinnitus. However, spontaneous firing rates in the MGB have also been found to be unaffected in rats with acoustic noise trauma or tinnitus (Barry et al., 2019). Most importantly, enhanced behavioral evidence of tinnitus pathology (i.e., increased z-scores of the raw-gap-startle in the GPIAs) was

linked to higher spontaneous firing rates, irrespective of sound exposure (Kalappa et al., 2014). The increases in spontaneous firing could be specified by increases in bursts per minute, in mean spikes per burst, and in overall burst duration (Kalappa et al., 2014). Taken together, this suggests a shift towards a more spontaneous hyperactive bursting pattern of MGB neurons, moreover LFP studies show an altered coherence in the MGB in tinnitus.

Human neuroimaging studies investigating the MGB in tinnitus

To the best of our current knowledge, intracranial or single-unit recordings from the MGB in humans do not exist. Paradigms investigating functionalities of the MGB in persons with tinnitus therefore often rely on measures of functional and structural connectivity obtained with fMRI (**Table 3**).

A large cross-sectional population-based study conducted in Japan identified an inverse relation between cerebral infarction in the thalamus and tinnitus, which could either be interpreted as cerebral infarctions inhibiting tinnitus or as increased tinnitus symptoms being present with no or reduced cerebral infarctions (Sugiura et al., 2008). Investigations of MGB volume in persons with tinnitus is generally in favor of similar MGB sizes in persons with tinnitus and controls (Landgrebe et al., 2009; Zhang et al., 2015), but opposing findings exist (Allan et al., 2016; Muhlau et al., 2006; Tae et al., 2018). Irrespective of hearing loss, diffusion tensor imaging (DTI) revealed that MGB connectivity was bilaterally reduced in persons with tinnitus (Gunbey et al., 2017). Another DTI study confirmed reduced white matter integrity in persons with tinnitus in the anterior thalamic radiation (Aldhafeeri, Mackenzie, Kay, Alghamdi, & Sluming, 2012), but opposing evidence exists, suggesting increased white matter integrity in the anterior thalamic radiation in persons experiencing tinnitus after noise induced hearing loss (Benson, Gattu, & Cacace, 2014). A task-based fMRI study investigated a group of persons with chronic tinnitus listening to music segments (Smits et al., 2007). When participants experienced bilateral tinnitus, signal change in the MGB was bilateral and if participants experienced tinnitus in the left ear, the right thalamus had a lower activation ratio (Smits et al., 2007). The reverse pattern (i.e., right tinnitus percept) was not significant, which is likely attributable to a smaller sample size. Another task-based fMRI study suggests reduced sound-evoked responses in the MGB in persons with tinnitus (Hofmeier et al., 2018).

Table 3. Human studies reporting effects on the auditory thalamus in tinnitus.

Study	Participants		Tinnitus duration	Tinnitus assessment	Control for HL	Paradigm	Method	Results auditory thalamus
	Ctrl	Tin						
Structural MRI								
Mülhau et al. 2006	28	28	> 4.5y	GHS	Yes[a]	structural lesions	MRI	Increased gray matter concentration in the MGB in tinnitus
Sugiua et al. 2008	1450	743	NA	Questionnaire	No	structural lesions	MRI	Inverse association between cerebral infarction and tinnitus
Functional MRI								
Smits et al. 2007	10	7 BLTin, 22 LTin, 13 RTin	> 5y	Pitch matching	No	task-based	fMRI	Symmetrical signal change in BLTin, Ltin decreased activation contralateral to Tin
Chen et al. 2014	32	32	> 3.4y	THQ	Yes	resting-state	fMRI (ALFF)	Decreased activity in bilateral thalamus
Zhang et al. 2015	33	31	> 3.5y	THQ	Yes[a]	resting-state	fMRI (VBM)	LThal = decrease in: MTG, mOFC, mFG,R PrecG, calcarine cortex; increase: angular gyrus, mCC, postCB; RThal = decrease in: STG, amygdala, SFG, L PrecG, mOG, increase: pCC, postCB; no changes in thalamic volume
Allan at al. 2016	55	73	min. 6 months	THI or THQ	Yes[b]	resting-state	fMRI (VBM, SBM)	Reduced white matter volume in the right MGB in severely affected tinnitus subgroup, reduced gray matter volume with increasing HL in the bilateral MGB; when comparing the subgroup Tin no HL vs HC, no effects in the MGB were found
Hofmeier et al. 2018	17	17	>4 weeks	GHS	Yes[a]	resting-state/task-based	fMRI	Reduced connectivity in the left MGB in tinnitus, reduced sound-evoked response in the MGB in tinnitus
Han et al. 2019	27	27	≥ 6 months	THI	Yes[a]	resting-state	fMRI (FCS)	Increased functional connectivity strength in the thalamus tinnitus compared to controls

Table 3. Continued

Study	Participants		Tinnitus duration	Tinnitus assessment	Control for HL	Paradigm	Method	Results auditory thalamus
	Ctrl	Tin						
Lv et al. 2020	25	25	> 2y	THI	Yes[a]	resting-state	fMRI	Increased connectivity between thalamus and IFG and ACC at baseline
Berlot et al. 2020	6	6	> 0.5y	TQ	Yes	resting-state/task-based	fMRI	Decreased connectivity starting at the MGB to higher auditory cortices
DTI								
Aldhafeeri et al. 2012	14	14	>6y	THI	Yes	Resting-state	DTI	Decreased white matter integrity in persons with tinnitus in the anterior thalamic radiation
Benson et al. 2014	13 NIHL	13 NIHL Tin	min. 6 months	THI	Yes	resting-state	DTI	Four clusters in the anterior thalamic radiation reflected increased white matter integrity for NIHL Tin
Gunbey et al. 2017	20	18 TinHL, 18 Tin	> 4y	THI, VAS	Yes	resting-state	DTI	Decreased connectivity in MGB in Tin patients
ECoG								
De Ridder et al. 2011	-	1 BLTin	14y	VAS	No	awake – resting-state	ECoG	Tinnitus-linked gamma-theta coupling, hypothesized to be influenced in thalamus
Sedley et al. 2015	-	1 BLTin	approx. 15y	THI	No	awake – task-based	ECoG	Tinnitus-linked delta oscillations, hypothesized to be triggered in thalamus

[a] In addition, controlled for hyperacusis.
[b] Forming subgroups from the original sample.
Abbreviations: ACC, Anterior cingulate gyrus, ALFF, Amplitude low-frequency fluctuations, BLTin, Bilateral tinnitus, Ctrl, DTI, Diffusion tensor imaging, Controls, ECoG, Electrocorticography, FCS, Functional connectivity strength, fMRI, Functional magnetic resonance imaging, GHS, Goebel-Hiller-Score tinnitus questionnaire, HC, Healthy controls, HL, Hearing loss, HQ, Hyperacusis questionnaire, IFG, Inferior frontal gyrus, LFP, Local field potentials, LTin, Left tinnitus, mCC, Medial cingulate cortex, mFG, Middle frontal gyrus, MGB, Medial geniculate body, mOFC, Medial orbitofrontal cortex, mOG, Middle occipital gyrus, MTG, Middle temporal gyrus, MRI, Magnetic resonance imaging, NIHL, Noise induced hearing loss, postCB, Posterior cerebellum, PrecG, Precentral gyrus, RTin, Right tinnitus, SBM, surface-based morphometry, STG, Superior temporal gyrus, THI, Tinnitus handicap inventory, Tin, Tinnitus, TinHL, Tinnitus with hearing loss THQ, Tinnitus handicap questionnaire, TQ, Tinnitus questionnaire, VAS, Visual analog scale, VBM, Voxel-based morphometry.

Resting-state fMRI in persons with tinnitus suggests overall decreased functional connectivity between the MGB and cortical regions. Han et al. (2019) found increased functional connectivity strength in the thalamus in persons with tinnitus compared to controls. Amplitude low-frequency fluctuations (ALFFs), a measure that has previously been related to spontaneous neural activity (Lv et al., 2018), was bilaterally decreased in the thalamus in persons with chronic tinnitus (Chen et al., 2014). There was a positive correlation between tinnitus duration and increases in ALFFs in the superior frontal gyrus (SFG) (Chen et al., 2014). Decreased functional connectivity between the left thalamus and right middle temporal gyrus (MTG), right middle OFC, left middle frontal cortex, right precentral gyrus was found in persons with chronic tinnitus (Zhang et al., 2015). When the right thalamus was used as a seed region, decreased functional connectivity between the right thalamus and the left superior temporal gyrus (STG), left amygdala, right SFG, left precentral gyrus, and left middle occipital gyrus was observed (Zhang et al., 2015). Conversely, increases in functional connectivity were observed between the thalamus and the posterior cerebellum, middle, and posterior cingulate cortices (Zhang et al., 2015). Taken together, these results confirm that the thalamus plays a central role in a wider thalamo-cortical network implicated in tinnitus pathology. However, Zhang et al. (2015) and Chen et al. (2014) did not differentiate between subcomponents within the thalamus (i.e., parts of the MGB), and it is noteworthy that decreased functional connectivity and increased spontaneous neural activity between the thalamus and SFG were observed in both experiments. Lv et al. (2020) investigated changes in functional connectivity before and after sound therapy. This study found higher connectivity measures at baseline for the tinnitus group between the thalamus, the inferior frontal gyrus (IFG; Brodman area (BA) 45), and the anterior cingulate cortex (ACC; BA 33), which were restored (i.e. decreased) after treatment (Lv et al., 2020). Reduced tinnitus severity could be associated with decreased functional connectivity between the right thalamus and the right IFG. Thus, the study of Lv et al. (2020) indicates increased functional connectivity for persons with tinnitus at baseline, whereas a different pattern (i.e. decrease in functional connectivity) for the superior and middle frontal gyrus was previously suggested by Zhang et al. (2015). Nevertheless, Lv et al. (2020) suggest that decreased functional connectivity may represent a decrease in attention in tinnitus pathology and a reduction in the involvement of the noise cancellation system (i.e. sensory gating) (Rauschecker et al., 2010), which supports the previously discussed findings. Another recent study focused on resting-state activity in persons with tinnitus (Berlot et al., 2020). Here, the MGB seed regions were chosen based on responses to the individual tinnitus frequency and to a control frequency, which had the farthest distance to the tinnitus pitch (i.e., using tonotopic maps from

each participant-control pair), while connectivity was measured along several centers of the auditory pathway. Results suggest reduced connectivity measures in persons with tinnitus starting at the level of the MGB (Berlot et al., 2020). Thus, in persons with tinnitus functional connectivity between the MGB and the primary auditory cortex and between the primary and the secondary cortices were reduced for the tinnitus and the control frequency seed (Berlot et al., 2020). These findings are in line with the findings reported by Zhang et al. (2015), suggesting reduced connectivity between the left thalamus seed and the right MTG.

Previously the inhibitory influence of the TRN on the MGB was incorporated in the noise-cancellation approach, stating that in persons without tinnitus, the TRN cancels out or filters unwanted sounds (Leaver et al., 2011; Rauschecker et al., 2010; Zhang, 2013). However, in persons with tinnitus, this filtering becomes distorted, leading to the perception of tinnitus (Leaver et al., 2011; Rauschecker et al., 2010; Zhang, 2013). To the best of our knowledge, there is only one human study investigating the TRN in tinnitus (Gunbey et al., 2017). Results by Gunbey et al. (2017) for the TRN parallel their findings for the MGB in persons with tinnitus this is reflected in decreased fractional anisotropy (FA) and increased apparent diffusion coefficient (ADC) values.

From the existing evidence, it can hence be concluded that functional connectivity between the auditory thalamus and auditory cortices (i.e., PAC, non-PAC) seems to be reduced in persons with tinnitus. In addition, there is increased connectivity between cingulate cortices, likely the IFG and posterior cerebellum, which indicates changes in the function of a widespread network due to disrupted thalamo-cortical functional connectivity (**Figure 2**). A recent study by Lin et al. (2020) compared topological network changes in gray matter between persons with tinnitus and controls using a graph-theoretical approach. Their betweenness centrality analyses revealed exclusive hubs in the amygdala and parahippocampus in persons with tinnitus, while hubs in the auditory cortex, insula, and the thalamus were exclusively present in controls but not in persons with tinnitus (Lin et al., 2020). The absence of the thalamus hub in the tinnitus group suggests altered interactions between the auditory thalamus and related auditory regions.

Currently, there are no invasive human MGB recordings available, but a limited amount of case studies performed intracranial cortical recordings in patients that also experienced tinnitus, which can be linked to alterations in the MGB. Two case studies investigated persons with tinnitus, while performing intracranial recordings from the (secondary) auditory cortex (i.e., electrocorticography, ECoG). Results from one study in a person suffering from severe tinnitus for 14 years showed increased gamma and

theta activity in one of the eight implanted electrode poles (De Ridder et al., 2011). Interestingly, the pole reflecting the enhanced gamma-theta coupling was located in an area that showed maximal BOLD activity levels in response to tones in the tinnitus frequency during an fMRI session (De Ridder et al., 2011). Lastly, intracranial measures recorded from the auditory cortex in a patient suffering from complex temporal lobe seizures suggest that tinnitus suppression (measured via residual inhibition) is linked to widespread delta band coherence (Sedley et al., 2015). Moreover, Sedley et al. (2015) observed increases in gamma (> 28 Hz) and beta2 (20-28 Hz) bands during tinnitus suppression. The authors identified three tinnitus sub-networks. The first is the large tinnitus-driven network characterized by changes in delta coherence in addition to delta, theta and alpha power changes. The second is the tinnitus memory network involved in auditory memory and mainly characterized by increases in alpha power.

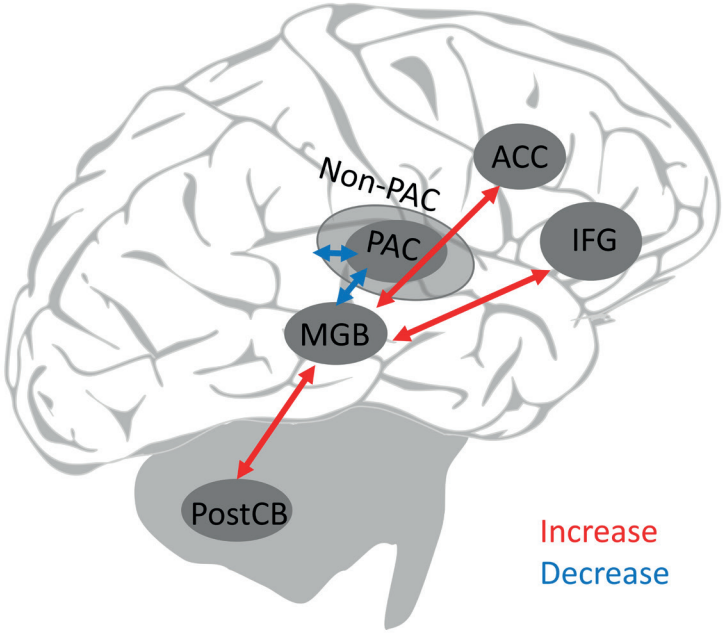

Figure 2. Summary and schematic representation of increased/decreased functional connectivity measures between the MGB and cortical areas. The representation is based on baseline measures of Lv et al., 2020, Berlot et al., 2020, and Zhang et al., 2015. Depicted are only areas with altered connections to the bilateral MGB. Zhang et al., 2015 observed decreased connectivity between the left thalamus to the medial frontal gyrus and the right thalamus and superior frontal gyrus, contrasting with increased connectivity between the MGB and the IFG (BA 45) by Lv et al., 2020. Zhang et al., 2015 further observed increased connectivity between the left thalamus and the middle cingulate cortex, and the right thalamus and the posterior cingulate cortex. ACC, Anterior cingulate cortex (BA 33), PAC, Primary auditory cortex, Non-PAC, Non-Primary auditory cortices, IFG, Inferior frontal gyrus, MGB, Medial geniculate body, PostCB, Posterior cerebellum. Lv et al. (2020), Berlot et al. (2020), Zhang et al. (2015).

The third network is the tinnitus perception network characterized by changes in the gamma and beta range (Sedley et al., 2015). Although these networks do not specifically focus on the functioning of the MGB, the authors note that the observed alterations in delta oscillations may be triggered by the thalamus.

Overarching framework: Linking animal and human findings and implementation in theoretical framework of temporal predictions

Due to fundamental methodological differences, the integration of results from animal studies investigating tinnitus and MGB functioning in humans faces several issues (for a summary of animal and human studies see **Table 1 and 2**). It is therefore important to evaluate the advantages and constraints of each method to draw conclusions about how to relate measurements at different functional levels to each other. Animal studies employ methods measuring single cell and multi-unit activity, or LFPs. These approaches allow drawing conclusions about neurotransmission, spontaneous firing rates, or coherence. In contrast, human studies report data obtained from large populations of neurons, or even whole brain analyses, with the thalamus increasingly being recognized as a seed region for connectivity analyses (Berlot et al., 2020; Lv et al., 2020; Zhang et al., 2015). As the MGB is a small subcortical structure, accessibility by means of high-temporal neuroimaging methods such as EEG/MEG to assess neural synchrony and coherence is severely limited. Therefore, resting-state functional connectivity or structural measurements are most common. Next to these methodological constraints, variability in tinnitus pathology is another critical factor. In animals, tinnitus is often induced using noise trauma or by administering sodium salicylate before behaviorally testing for tinnitus using either interrogative or reflexive models (i.e., GPIAS). While sodium salicylate was found to reliably induce tinnitus (Day et al., 1989; Lobarinas, Sun, Cushing, & Salvi, 2004; Stolzberg, Salvi, & Allman, 2012; Su et al., 2012), affective components such as anxiety or stress are typically not considered (Brozoski & Bauer, 2016; Kleinjung & Langguth, 2020). In addition, the type of tinnitus induced with sodium salicylate is quite different when compared to the poise induced model, as tinnitus experience after receiving sodium salicylate is more intense and not accompanied by hearing loss, which could occur when administering a noise trauma (Norena, Moffat, Blanc, Pezard, & Cazals, 2010). The GPIAS model on the other hand has been criticized to not be transferable to humans, because in humans gap detection thresholds were similar for persons with tinnitus and controls (Clayton & Koops, 2021; Zeng, Richardson, & Turner, 2020). In humans, tinnitus pathology is heterogeneous as

well (Cederroth et al., 2019; Kleinjung & Langguth, 2020). For instance, persons with tinnitus differ with respect to perceptual characteristics, time course, comorbidities and response to interventions (Kleinjung & Langguth, 2020). The identification of reliable tinnitus subtypes therefore remains a major challenge (Cederroth et al., 2019; Kleinjung & Langguth, 2020). In general, tinnitus is likely preceded by peripheral hearing loss and most persons with tinnitus have abnormal audiograms. However, several issues remain, as for example, most people experiencing hearing loss does not develop tinnitus (Roberts, Moffat, & Bosnyak, 2006; Sedley, 2019). Of note that peripheral hearing loss leads to deafferentiation at the level of the cochlear, but that even without behaviorally measurable hearing loss, deafferentaition is probably still present in persons with tinnitus (Weisz et al., 2006). Another unresolved paradox is that the development of tinnitus is difficult to explain by either a pure peripheral or central model, although, even though tinnitus is thought to be initialized by peripheral hearing loss (Sedley et al., 2016). Therefore, to bridge the gap between the results obtained by animal models and human studies, additional research is clearly needed to link the underlying mechanisms to the known functional characteristics of the auditory thalamus.

Thalamo-cortical dysrhythmia and sensory gating in tinnitus

Several theoretical approaches attempted to explain the development of tinnitus (for an overview see: Sedley et al. (2016)). However, only a few specifically account for MGB function. The noise cancellation approach for instance, proposes interactions between limbic structures and the auditory thalamus in tinnitus pathogenesis in a top-down fashion (Rauschecker et al., 2010; Song, Vanneste, & De Ridder, 2015). Healthy individuals engage the non-classical auditory pathway to evaluate the emotional content of sound stimuli in parallel to auditory processing along the classical auditory pathway. Unpleasant auditory input is normally “cancelled out” at the level of the MGB (Rauschecker et al., 2010). In persons with tinnitus, however, the noise cancellation (i.e., sensory gating) mechanism is dysfunctional, leading to disinhibition of the MGB, possibly contributing to the perception of a tinnitus sound (Elgoyhen et al., 2015). Sensory gating may also be conceived as an adaptive mechanism that is employed to filter out irrelevant information based on spectral and temporal information to predictively adapt and optimize auditory function (Schwartze & Kotz, 2013).

Another approach suggests that distorted firing patterns and altered oscillatory coupling mechanisms at the level of the MGB may induce tinnitus in a bottom-up fashion (De Ridder et al., 2015; Llinás et al., 1999). The thalamo-cortical dysrhythmia hypothesis suggests aberrant neural synchrony within and between the thalamus and

cortex. Decreased auditory input leads to altered rhythmic burst firing in the MGB (i.e. increased low-frequency thalamic oscillations, triggered by LTS), which leads to increased activation in higher auditory cortices in theta, delta and gamma ranges (De Ridder et al., 2015; Llinás et al., 1999). De Ridder et al. (2015) speculate that in tinnitus with limited deafferentiation, alpha oscillations slow down and turn into theta oscillations, which are coupled to gamma oscillations, while gamma has been interpreted as the bottom-up transmitted prediction error. In severe deafferentiation, however, auditory information retrieval might be mediated by parahippocampal auditory memories acting in the theta range (De Ridder et al., 2015). Altered high frequency activity in the dorsal ACC or pregenual anterior cingulate might represent allostasis processes involved in a reference resetting, indicating that the new norm state might be the tinnitus state and not the silent state (De Ridder et al., 2015). Theta is suggested to act as a carrier frequency, needed to activate the tinnitus network, while gamma encodes the tinnitus intensity (De Ridder et al., 2011; De Ridder et al., 2015).

Support for dysfunctional sensory gating mechanisms in the thalamus in persons with tinnitus was recently provided by Lin et al. (2020), showing in a graph-theoretical approach that the thalamus hub was only present in the control group and not in persons with tinnitus. Eliciting tinnitus-like symptoms using an auditory illusion in healthy young adults without hearing loss, resulted in enhanced total theta power in the parahippocampus, pregenual ACC, the ventro-medial PFC and OFC, further supporting inadequate sensory gating even in healthy participants (Mohan et al., 2020). The concept of sensory gating allows linking the intrinsic firing modes of the thalamus, the top-down noise-cancellation approach (Rauschecker et al., 2010) and the bottom-up thalamo-cortical dysrhythmia approach (De Ridder et al., 2015; Llinás et al., 1999) into a common theoretical framework for predictive adaptation.

The functional principle of sensory gating (i.e., the filtering out of irrelevant information) has been associated with reduced neural activity for predicted information (i.e. gating out) and increased activity for unpredicted information (i.e., gating in) (Grunwald et al., 2003; Marshall, Bar-Haim, & Fox, 2004; Pratt, Starr, Michalewski, Bleich, & Mittelman, 2008; Schwartze & Kotz, 2013). Schwartze and Kotz (2013) introduced an integrative subcortico-cortical network for feature-based and temporal predictions. Feature-based information (used to generate “what” predictions based on the formal structure of a dynamic input) is primarily encoded linearly (i.e., engaging thalamic tonic firing), whereas temporal information (used to generate “when” predictions based on salient input features such as onsets, offsets, and rising energy contours) are encoded non-linearly (i.e., engaging thalamic burst firing) in the MGB. The resulting dual-pathway neural

architecture for specific temporal prediction may provide a common framework for understanding how alterations in the MGB could translate to the experience of tinnitus (**Figure 3**). Reduced sensory gating (i.e., reduced inhibition) at the level of the cortex, as suggested by the noise-cancellation approach, the thalamo-cortical dysrhythmia approach and by the increases in spontaneous firing rates at the level of the MGB may be key to guide understanding of the role of the MGB in tinnitus pathology.

Sensory gating in the MGB and temporal stimulus predictability

Tinnitus has previously been associated with predictive coding (De Ridder et al., 2015; Hullfish, Sedley, & Vanneste, 2019; Sedley et al., 2016). (Latent) prediction errors are likely represented by gamma oscillations. Attention, memory and learning towards the tinnitus experience might modulate the influence of prediction errors at higher functional levels (Sedley et al., 2016). Sedley and colleagues suggest that high frequency gamma oscillations convey bottom-up prediction errors that are compared to top-down predictions, involving lower frequency beta oscillations (Sedley et al., 2016). Low-frequency oscillations, especially in the theta range, have been suggested to function as carriers, while being able to modulate high-frequency oscillations (Canolty et al., 2006). Hullfish et al. (2019) further suggest that differential predictive mechanisms might underlie acute or chronic tinnitus. Moreover, increased mismatch negativity responses (MMN) were observed in persons experiencing tinnitus, indicating violated sensory predictions (Sedley et al., 2019). However, it may still be necessary to further differentiate temporal and formal aspects of predictions in relation to MGB functioning. Here we suggest that alterations in the thalamic firing modes, likely caused by tinnitus, contribute to the observed changes in oscillatory activity in higher cortical auditory areas. As it is proposed that sensory gating (e.g. gating out the predicted stimuli in a paired-stimulus paradigm) is dysfunctional in tinnitus (Bayazitov et al., 2013; Lin et al., 2020), we propose that sensory gating at the level of the MGB can be differentially influenced by altering the temporal and formal predictability of the input signal.

It is possible that there is a direct input route for auditory sensory processing to the cerebellum, as suggested by an ALE meta-analysis by Petacchi, Laird, Fox, and Bower (2005). In addition, research in the cat auditory system supports direct connections between the cochlear nucleus and the cerebellum (Huang & Burkard, 1986; Huang, Liu, & Huang, 1982). Rapid cerebellar transmission is suggested to encode event-based temporal information (Schwartze & Kotz, 2013; Teki, Grube, & Griffiths, 2011; Teki, Grube, Kumar, et al., 2011), triggering a burst firing mode (i.e. non-linear) in the thalamus (**Figure 3A**). In other words, the cerebellum receives auditory input

and transmits successive events via the thalamus to frontal areas, mimicking a "clock signal". The basal ganglia encodes the relation (i.e. the interval-based timing) between events and feeds this information back to frontal areas (Allman & Meck, 2012; Schwartze & Kotz, 2013; Teki, Grube, & Griffiths, 2011; Teki, Grube, Kumar, et al., 2011). The auditory cortex is connected to frontal cortices, while receiving input from parahippocampal areas for memory retrieval, as suggested by De Ridder et al. (2015) and Schwartze and Kotz (2013). Moreover, the frontal cortex feeds information about stimulus identity and interval duration back to the basal ganglia (Matell, Meck, & Lustig, 2005). In persons with tinnitus however, signal encoding is less efficient. Animal and human studies have shown altered connectivity between the MGB and cortical areas, and increased bursting and spontaneous firing rates in the MGB itself, leading to less precise predictive adaptation. The connectivity between the MGB and the primary and secondary auditory cortex is probably reduced (**Figure 3B**).

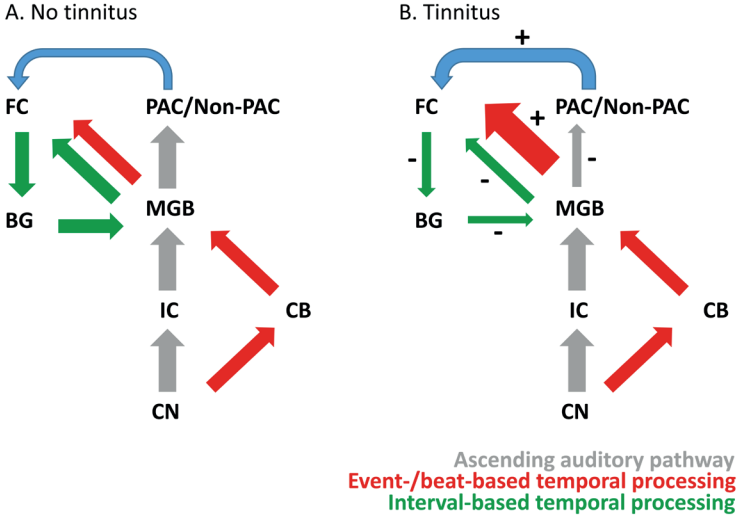

Figure 3. Schematic representation of the neural architecture for specific temporal prediction in persons without tinnitus (A) and with tinnitus (B). Here, the ascending auditory pathway does not distinguish between the classical and the non-classical auditory pathway. The schema does not depict predictive top-down modulation of the network by dynamic input. The MGB forms a major hub in transmitting a timing signal to higher cortical areas (event-/beat-based temporal processing (red)). This signal forms the basis for interval-based temporal processing (green) in BG circuits. Parallel activation and integration of memory representations recruit connections between temporal and frontal cortices (blue). In tinnitus (B), connections between the MGB and auditory cortices are reduced. Starting from the MGB, increased burst and spontaneous firing leads to an increase in event-/beat-based temporal processing. Tonic firing is proposed to be reduced, reflected by decreased interval-based temporal processing, as depicted by the different arrow sizes + and – signs. In severe deafferentation, memory retrieval increasingly relies on parahippocampal and auditory areas. PAC/Non-PAC, Primary and non-primary auditory cortices, BG, Basal ganglia, CB, Cerebellum, CN, Cochlear nucleus, FC, Frontal cortex, IC, Inferior colliculus, MGB, Medial geniculate body.

In addition, as increased bursting in the MGB has been observed in persons with tinnitus, increased event- or beat-based processing may be observed starting from the thalamus, while the processing interval-based durations might be reduced. Especially in severely affected persons, memory retrieval from parahippocampal areas probably strengthens the association between the auditory cortices and frontal areas. Manifestations of the described alterations in this neural architecture for specific temporal predictions might be observed by increases in gamma and slow frequency bands such as theta or delta, as suggested by work from Sedley and colleagues or De Ridder et al. (2015) and by dysfunctional sensory gating mechanisms in persons with tinnitus (see for example: Schwartze et al. (2013); Schwartze, Rothermich, et al. (2011)). However, it still needs to be elucidated if it is possible to influence and eventually optimize synchronization between the thalamus and the auditory cortices, to ultimately compensate for the thalamo-cortical dysrhythmia by altering the rhythmical structure of the input signal. Compensation of the thalamo-cortical dysrhythmia would allow treating tinnitus at the level of the MGB and to reinstate its functionality.

Conclusion

Based on the limited number of studies investigating MGB functioning in tinnitus pathology and their overall heterogeneous approaches, it can be concluded that tinnitus is associated with increased spontaneous firing in the MGB, decreased functional connectivity between the MGB and a widespread thalamo-cortical network, in addition to decreased connectivity between the MGB and auditory cortices. Decreased functional connectivity between the MGB and auditory cortices can lead to reduced inhibition at the level of the auditory cortex. Parallel increased functional connectivity between the ACC and the IFG and the MGB may represent dysfunctional attentional processes or allostatic mechanisms. Similarly, altered patterns of oscillatory activity have been observed between the MGB and cortical areas, mainly expressed as increased activity in high frequency gamma and beta bands, decreased activity in delta bands, and altered theta and alpha coherence, providing support for the thalamo-cortical dysrhythmia hypothesis. However, the existence and contribution of several local sub-networks to the development and maintenance of tinnitus, as suggested by Sedley et al. (2015), should not be neglected. Here we link changes in thalamic firing modes and oscillatory bands to tinnitus. We suggest that these changes modulate the function within a neural architecture mediating predictive adaptation of an organism to the auditory environment. Modulation of temporal characteristics of input signals might influence this neural architecture for predictive adaptation, likely altering the tinnitus experience. Therefore, modulation of temporal characteristics could ultimately help establish new directions for treatment options for persons with tinnitus.

3

Chapter 3

About time: Ageing influences neural markers of temporal predictability

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Abstract

Timing abilities help organizing the temporal structure of events but are known to change systematically with age. Yet, how the neuronal signature of temporal predictability changes across the age span remains unclear. Younger (*n* = 21; 23.1 years) and older adults (*n* = 21; 68.5 years) performed an auditory oddball task, consisting of isochronous and random sound sequences. Results confirm an altered P50 response in the older compared to younger participants. P50 amplitudes differed between the isochronous and random temporal structures in younger, and for P200 in the older group. These results suggest less efficient sensory gating in older adults in both isochronous and random auditory sequences. N100 amplitudes were more negative for deviant tones. P300 amplitudes were parietally enhanced in younger, but not in older adults. In younger participants, the P50 results confirm that this component marks temporal predictability, indicating sensitive gating of temporally regular sound sequences.

Introduction

Timing abilities are central to our subjective experience of the temporal course of events (Allman & Meck, 2012). For example, when parking a car, a parking assistant helps to estimate the distance of objects using auditory feedback. With sufficient distance to an object, this feedback is a repeated tone presented at temporally regular intervals. However, when approaching an obstacle, tones increase in rate and pitch, attracting attention and optimizing reactions (Nobre & Van Ede, 2018). By changing its temporal structure (i.e., increasing rate) and formal structure (i.e., increasing pitch), the isochronous rhythm of the parking assistant thus signals a potential danger. While the formal structure of a stimulus defines an event type (Schwartze et al., 2013), i.e., "what" is perceived, the temporal structure refers to "when" an event occurs (Fraisse, 1984). Accurate timing abilities may allow predicting "when" something is likely to happen and may complement predictions about "what" can be expected (i.e., formal structure; (Nobre & Van Ede, 2018; Schwartze et al., 2013; Schwartze, Rothermich, et al., 2011). It is known that timing abilities contribute to successful adaptive behavior, such as changing the focus of attention (Nobre, Correa, & Coull, 2007; Nobre & Van Ede, 2018). Efficient adaptation to a dynamic environment requires extrapolation from past events to predict future events (Nobre et al., 2007; Nobre & Van Ede, 2018). Here, the primary focus was on temporal predictability in temporally manipulated auditory sequences.

At the neural level, the dissociation of formal and temporal structure can also be translated to patterns of oscillatory activity. Neural oscillations occur naturally in the brain, indicating transient rhythmic variations in the excitability of neuronal populations (Canolty & Knight, 2010; Lakatos, Chen, O'Connell, Mills, & Schroeder, 2007). They can be described in terms of repetition rate (i.e., frequency), amplitude (i.e., magnitude) and phase (i.e., a position within a wave cycle; (Canolty & Knight, 2010; Kotz, Ravignani, & Fitch, 2018; Large & Jones, 1999)). Entrainment of oscillatory activity describes a state in which such activity becomes aligned with external stimulation (i.e., via period and phase adjustment), for example, a periodic auditory rhythm (Kotz et al., 2018; Large, 2008; Large & Kolen, 1994). Entrainment to rhythmic stimulation has also been proposed to modulate attentional processes. Dynamic Attending Theory (DAT; Large & Jones, 1999) suggests that the allocation of attention is partly driven by the temporal properties of sensory input. According to this theory, internal attending rhythms entrain to external stimulation, thereby generating expectations regarding the future course of events (Jones, 1976; Jones, 2018; Large & Jones, 1999). Note that the processing of temporal structure can be examined in both perceptual and sensorimotor tasks.

To gain a better understanding of the neural mechanisms underlying temporal structure and temporal predictability, thorough investigation of the diseased or ageing brain are needed. The general importance of sensory and sensorimotor timing abilities becomes evident when underlying mechanisms are affected by neural or psychological conditions, such as Parkinson's Disease (Benoit et al., 2014; Cunnington, Iansek, Bradshaw, & Phillips, 1995), schizophrenia (Carroll, Boggs, O'Donnell, Shekhar, & Hetrick, 2008), attention-deficit hyperactivity disorder (Dankner, Shalev, Carrasco, & Yuval-Greenberg, 2017; Hart et al., 2014), cerebellar (Ivry & Keele, 1989; Kotz, Stockert, & Schwartze, 2014) or basal ganglia lesions (Schwartze, Keller, Patel, & Kotz, 2011). For example, timing abilities are compromised in Parkinson's disease patients (Allman & Meck, 2012; Benoit et al., 2014; Dalla Bella et al., 2017; Puyjarinet et al., 2019), leading to impaired temporal predictions (Breska & Ivry, 2018). However, there are also indications that timing abilities vary over the lifespan and change systematically with age (McAuley et al., 2006). Finger tapping tasks in the absence of a pacing stimulus indicate that the chosen rates slow down with increasing age (Vanneste, 2001). Average spontaneous inter-tap intervals (ITIs) are about 300 ms in children. Younger adults prefer slower rates (~600 ms ITI) , while this rate is more variable and further slowed down to about 650 ms in older adults (> 75 years of age; McAuley et al., 2006). In the present study, the emphasis was on the influence of age on temporal predictability.

Age-related changes in timing abilities have been investigated at the neural level by event-related potentials (ERPs), measures of oscillatory activity, and neural entrainment. Henry and colleagues (2017) investigated entrainment patterns in younger and older participants who had to detect a gap in frequency modulated sound sequences. Results indicated that oscillations in older adults entrained less strongly and less adaptively to the target frequency than in younger adults (Henry et al., 2017). Another study focused on the effects of different types of temporal structure on neural entrainment and found reduced entrainment in the vicinity of the target frequencies in older adults, as reflected by decreased mean spectral amplitudes (Sauvé, Bolt, Fleming, & Zendel, 2019).

ERP studies also provide evidence for differential neural activity associated with temporal predictability across different ages. The auditory P50, N100, P200 and P300 components are sensitive to manipulations of temporal and formal structure (Schwartze et al., 2013; Schwartze, Rothermich, et al., 2011). The middle-latency P50 is a positive ERP deflection that peaks around 50 ms after sound onset, known to be generated in temporal areas, and functionally interpreted as a marker of sensory gating (Korzyukov et al., 2007; Smith, Boutors, & Schwarzkopf, 1994). Sensory gating can be described as a filter of sensory auditory information, where impaired filter mechanisms lead to the

unfiltered transmission of auditory information to higher-order brain areas (Korzyukov et al., 2007). Source localization analyses suggest that next to temporal areas, P50 is generated in frontal regions of the brain (Korzyukov et al., 2007). Age effects in classical paired-stimulus paradigms were observed at inter-stimulus intervals (ISI) of 250 ms, suggesting P50 suppression in older but not in younger participants (Rasco, Skinner, & Garcia-Rill, 2000). Another study reported an increased P50 amplitude response with increasing age, based on results obtained with an oddball paradigm (Golob, Irimajiri, & Starr, 2007). Moreover, P50 activity was modulated by manipulations of temporal and formal structure in a sample of younger adults (Schwartze et al., 2013). Taken together, previous research suggests that P50 may serve as a marker of temporal predictability, with overall increased amplitudes observed in older participants.

The N100 is a long-latency negative ERP deflection that peaks approximately 100 ms in response to a sound onset and is generated in the supratemporal planes of the auditory cortex (Näätänen & Picton, 1987). The N100 can be observed after unpredicted stimuli (Schafer & Marcus, 1973) and also distinguishes between self- and other-generated auditory events via amplitude suppression in the former case (Baess, Jacobsen, & Schröger, 2008; Knolle, Schröger, Baess, & Kotz, 2012; Knolle, Schwartze, Schröger, & Kotz, 2019). Previous ERP studies by Schwartze and colleagues used a paradigm that independently manipulated formal and temporal structure in auditory sequences to investigate temporal predictability (Schwartze et al., 2013; Schwartze & Kotz, 2015; Schwartze, Rothermich, et al., 2011). In this paradigm, two different sound sequences were utilized. The first sequence followed an isochronous rhythm (i.e., a regular temporal structure), while containing two tones differing in formal structure (i.e., in pitch). The other sequence followed a random temporal structure, while containing identical tones. When recording responses to manipulations of temporal and formal structure in a sample of younger adults, N100 activity patterns did not differentiate between changes in temporal structure (i.e., isochronous versus random), but formal structure (i.e., standard versus deviant; Schwartze, Rothermich, et al. (2011)). Interestingly, older adults seem to exhibit shorter N100 latencies than younger adults in auditory oddball paradigms (Golob et al., 2007). These findings suggest that ERP latencies shorten with increasing age (Tomé, Barbosa, Nowak, & Marques-Teixeira, 2015). However, there are also indications that the N100 amplitude is not affected by age in attentive conditions, but increases in pre-attentive conditions (Schiff et al., 2008). Further results indicate that N100 latency does not differ in attentive and pre-attentive conditions (Schiff et al., 2008), suggesting that N100 is less affected by age than other components, for example the later P300 complex (Schiff et al., 2008).

The P200 component is a positive ERP deflection peaking at approximately 200ms after the presentation of an auditory stimulus and is detectable at anterior and central sites (Luck, 2014). Like the P300 complex, the P200 is larger for deviant stimuli in an oddball paradigm. It has been suggested that while the P200 is elicited only by simple stimulus features, the P300 could be elicited by more complex stimulus features (Luck, 2014). Previous research on temporal predictability and the P200 in younger adults found reduced P200 deflections for more temporally predictable cue-target trials (Herbst & Obleser, 2017).

The P300 complex is a positive deflection, generated in centro-parietal areas, and peaks approximately 300ms after the presentation of an auditory stimulus (Polich & Criado, 2006). In oddball paradigms, the P300 component has long been studied and can be divided between the more frontally located P3a and the more parietally located P3b (Squires et al., 1975). While both sub-components are elicited by infrequent and unpredictable changes, the P3b is only present when changes are task-relevant (i.e., participants count the number of deviants in a stimulus sequence) and is referred to as the P300 component. A related study by Schwartze, Rothermich, et al. (2011) investigated the effect of formal structure in an oddball paradigm and assessed P3b activity in an attentive session. When comparing younger with older adults, reduced P300 amplitudes and delayed latencies were observed in the latter, using an oddball paradigm (Golob et al., 2007; Nowak et al., 2016). Notably, in the study by Golob et al. (2007), P300 latencies progressively increased from healthy elderly to patients diagnosed with mild cognitive impairment and mild Alzheimer's disease.

In summary, previous evidence suggests an effect of age on EEG markers of temporal predictability and deviance processing. Based on previous research, it is suggested that P50 is modulated in younger adults by temporal (i.e., isochronous versus random sequences) and formal structure in oddball paradigms (Schwartze et al., 2013). Previous observations suggest increased P50 amplitudes with increasing age. Second, the amplitude of the N100 seems to be sensitive to formal but less or not to manipulations of temporal structure. Moreover, it is suggested that P300 amplitudes decrease, and latencies increase for older relative to younger adults. However, the existing studies did not systematically investigate age-related effects, while directly manipulating the temporal (i.e., temporal predictability by comparing isochronous with random sequences) and formal structure (i.e., standard versus deviant tones) in an oddball paradigm. The advantage of directly manipulating temporal regularity in auditory oddball sequences is to better isolate temporal predictability regarding structural predictability and to pinpoint its neural underpinnings across age groups.

The goal of the present study was to shed light on the effect of age on the underlying neural correlates of temporal predictability measured with EEG. We hypothesized that (1) ERP amplitudes and latencies would be differentially modulated by formal and temporal structure and that, P50 may serve as marker of temporal predictability; (2) that P50 amplitudes will be increased, N100 latencies will be altered and P300 amplitudes and latencies decreased for older adults compared to younger ones. Investigating the effect of age on neural correlates of temporal predictability will expand the current knowledge about systematic changes of timing abilities during ageing.

Methods and Materials

Participants and recruitment

A group of younger adults (*n* = 21, 8 males, *Mage* = 23.1 years, age range: 18-29 years) and a group of older adults (*n* = 21, 6 males, *Mage* = 68.5 years, age range: 59-80 years) participated in the study. All participants were right-handed. Two participants in the younger group were excluded from the analysis, one due to left-handedness and one due to low signal quality (> 70% of the data had to be removed after artefact correction procedures). All participants (*N* = 42) were non-musicians (i.e., with less than 2 years of formal musical training). Recruitment took place via advertisements, presentations in community centers, elderly homes, and word of mouth. Participants did not have a history of alcohol or drug abuse, did not take medications acting on the nervous system, or had previous head trauma, neurodevelopmental disorders, psychopathology and visual, hearing, or motor disabilities. The study was approved by the *Comité d'éthique de la recherche en éducation et en psychologie* (CEREP) of the University of Montréal (UdeM) and adhered to the Declaration of Helsinki. Written consent was obtained, and participants were reimbursed with 10$/h.

EEG Task, Data Acquisition, Preprocessing and ERP Analysis

EEG task

The experimental EEG paradigm employed consisted of an adaptation of a previously established oddball paradigm (Schwartze et al., 2013; Schwartze & Kotz, 2015; Schwartze, Rothermich, et al., 2011). The paradigm comprised two oddball sequences that differed in their temporal structure, i.e., the ISI was either fixed (ISI = 1000ms; isochronous sequence) or varied randomly between 600ms and 1400ms (average ISI = 1000ms; random sequence), while keeping the duration of each auditory stimulus constant (150ms, 10ms rise and fall). Each sequence contained 721 tones (deviant =

144, standard = 577). Thus, in total 1442 tones were presented, 1154 standard (600 Hz), and 294 oddball (660 Hz) sinusoidal tones (ratio of 4:1; **Figure 1**). To ensure that the participants focused on the task to count the number of deviants, deviants were added to the sequence that was presented last (i.e., deviant = 147, standard = 577). Due to counterbalancing, the order of presentation switched from presenting isochronous - random to random - isochronous sequences. Those additional deviants were not further considered during analysis.

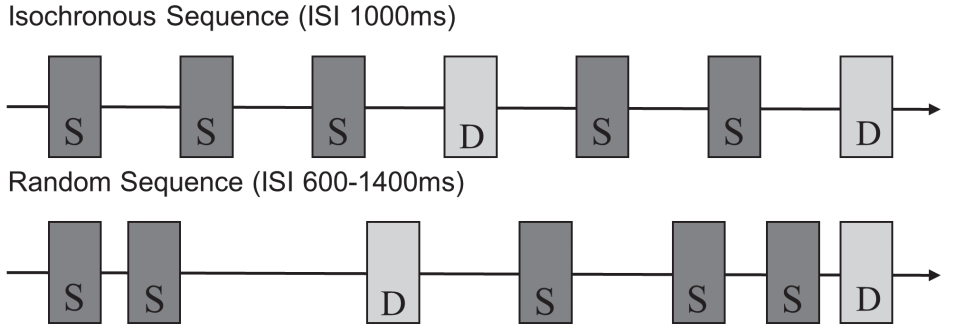

Figure 1. Examples of the two stimulus sequences. S = Standard, D = Deviant, ISI = inter-stimulus-interval.

Participants were asked to fixate an asterisk displayed on a computer screen, to count the number of deviants in each sequence, and to report the respective number at the end of each sequence. Stimuli were presented via insert earphones using Presentation software (NeuroBehavioral Systems, NBS). The presentation of the tones was pseudorandomized, to warrant that each sequence started with four standard tones to establish a memory trace and that maximally two deviants were presented consecutively. The order of the sequences was counterbalanced to avoid carry-over effects.

EEG data acquisition and preprocessing

A Biosemi ActiveTwo system was used to record continuous EEG data. Reference free brain activity from 64 channels, arranged according to the international 10-20 system (Sharbrough, 1991) and grounded to a two electrode feedback loop was recorded at a sampling rate of 1024 Hz. Six additional electrodes were bilaterally placed at mastoid and lateral ocular sites and unilaterally inferior to one eye and on the nose. Impedances were kept below 5 kOhms.

Preprocessing was performed using EEGlab (Delorme & Makeig, 2004) and the ERPLab toolbox (Lopez-Calderon & Luck, 2014), following Makoto Miyakoshi's preprocessing pipeline. The data were first down-sampled to 256 Hz, then a high-pass filter (0.1 Hz) was applied. In the following, the plug-in *clean_rawdata* was used to remove bad channels, which were then interpolated from the original dataset (Mullen et al., 2015). Re-referencing was performed to the average and the plug-in *CleanLine* was used to eliminate line noise (Mullen, 2012). To remove muscular and ocular artefacts, independent component analyses (ICA) were applied (Delorme & Makeig, 2004). After baseline correction, epochs starting–200 ms before stimulus onset and ending 535 ms post-stimulus were segmented for each stimulus (standard and deviant tones). Three additional steps of artifact rejection were performed. First, epochs exceeding ± 40 μV were excluded. Then a 100 μV thresholder using a moving window peak to peak was used to exclude remaining epochs containing blinks. Finally, a 30 μV thresholder for detecting step-like artifacts was used to remove trials containing remaining horizontal ocular movements. On average, 10% of trials were rejected (older adults = 13.9%, younger adults = 6.1%).

ERP analysis

Nine regions of interest (ROIs) for further analysis were selected based on Schwartze et al. (2013) and Schwartze, Rothermich, et al. (2011), as the current research consisted of an adapted version of the same paradigm. The ROIs were left-anterior (AF7, AF3, F7, F5, F3, Fp1), left-central (T7, C5, C3, TP7, CP5, CP3), left-parietal (P7, P5, P3, PO7, PO3, O1), medial-anterior (Fz, FCz, F1, F2, FC1, FC2), medial-central (Cz, C1, C2, CPz, CP1, CP2), medial-parietal (Pz, P1, P2, POz), right-anterior (AF8, AF4, F8, F6, F4, Fp2), right-central (T8, C6, C4, TP8, CP6, CP4), right-parietal (P8, P6, P4, PO8, PO4, O2). We expected the P50, N100 and P200 components in fronto-central regions, while for the P300 the centro-parietal ROIs were focused on (Korzyukov et al., 2007; Linden, 2005; Polich & Criado, 2006). After visual inspection of the grand averages and individual waveforms, the following time-windows were selected for the respective four ERP components: 35-70 ms (P50), 75-130 ms (N100), 150-220 ms (P200) and 250-525 ms (P300). Variables of interest extracted from these time-windows were local mean amplitudes and local peak latency values in the specified time windows. Please note that we also analyzed the data using different approaches of applying temporo-spatial PCAs (tsPCA). We performed one tsPCA on conditions and groups combined, as well as 8 tsPCAs, separate per stimuli. Overall, the results were like the ones that are reported here.

Statistical Analyses

Mixed-design 2 Group (younger versus older adults) x 2 Temporal structure (isochronous versus random sequences) x 2 Formal structure (standard versus deviant tones) x 3 Hemisphere (left versus medial versus right) x 3 Region (anterior versus central versus parietal) ANOVAs were performed per ROI, separately for amplitude and latency values. Group was the between-subject factor, Temporal- and Formal structure, Hemisphere and Region were the within-subject factors. When needed, Greenhouse-Geisser correction was applied to the results reported. Post-hoc analyses consisted of paired t-tests, if necessary, performed after averaging across non-significant factors and were Bonferroni corrected. A thresholder of $p = .05$ indicated statistical significance.

Results

First, to ensure that participants paid attention to the task, one-sample t-tests were performed on the results of the counting task. There were no significant differences between the number of stimuli to be counted and the numbers reported by the participants for the isochronous (number of stimuli to be counted: 147, $M = 144.65$, SD = 14.41, $t(1,42) = -1.07$, $p = .291$) and the random sequence (number of stimuli to be counted: 147, $M = 149.86$, SD = 23.41, $t(1,42) = .801$, $p = .428$) confirming that participants paid attention to the sequences.

P50

Results and topographical maps for the P50 are presented in **Figure 2** for younger **(Figure 2A)** and older adults **(Figure 2B)**. Although no significant main effect for Temporal structure was found ($F_{(1, 40)} = .66$; $p = .422$, $\eta^2_{partial} = .016$), main effects of Group ($F_{(1, 40)} = 4.98$; $p = .031$, $\eta^2_{partial} = .111$), Formal structure ($F_{(1, 40)} = 13.71$; $p = .001$, $\eta^2_{partial} = .255$), Region ($F_{(2, 80)} = 71.46$; $p < 001$, $\eta^2_{partial} = .641$) and Hemisphere ($F_{(2, 80)} = 5.83$; $p = .005$, $\eta^2_{partial} = .127$) were further qualified by multiple interactions, including a significant interaction between all five factors ($F_{(4, 160)} = 4.81$; $p = .002$, $\eta^2_{partial} = .107$). As we expected the P50 to be most prominently displayed in fronto-central regions (Bak, Glenthoj, Rostrup, Larsson, & Oranje, 2011), post-hoc analyses for the medial-anterior ROI were performed and indicated, specifically for the younger group, larger amplitudes ($M = 0.582$ µV) for deviant tones as opposed to standard ones ($M = 0.314$ µV) in the random sequence ($t_{(20)} = 3.02$, $p = .007$). The difference between deviant and standard tones for the isochronous sequence was non-significant ($t_{(20)} = 1.63$, $p = .119$) in the younger group. Increased amplitudes for standard tones when comparing the random ($M = 0.314$ µV) and isochronous ($M = 0.132$ µV) sequences were observed

in the younger group ($t_{(20)}$ = -2.82, p = .011). For deviant tones the difference between the isochronous and random sequence was not significant in the younger group ($t_{(20)}$ = -2.38, p = .081; Bonferroni corrected). For the older group, no significant differences were observed for the post-hoc analyses (Formal structure in isochronous sequence: $t_{(20)}$ = 1.75, p = .096; Formal structure in random sequence: $t_{(20)}$ = -.041, p = .967; Temporal structure for deviant tones: $t_{(20)}$ = .799, p = .434; Temporal structure for standard tones: $t_{(20)}$ = -.987, p = .335).

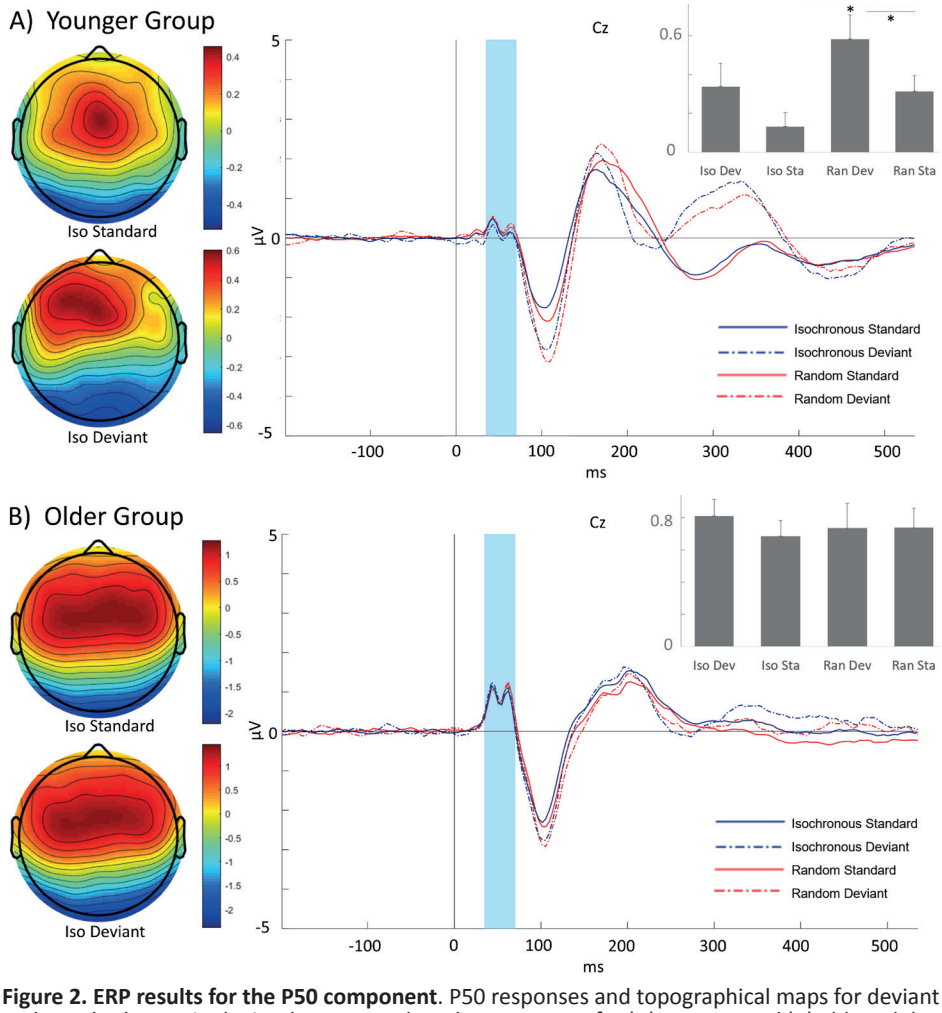

Figure 2. ERP results for the P50 component. P50 responses and topographical maps for deviant and standard tones in the isochronous and random sequence for (**A**) younger and (**B**) older adults. The bar plot reflects local mean amplitudes of the medial-anterior ROI.

The local peak latency measures of the P50 did not show a main effect of Group ($F_{(1, 40)}$ = .6; p = .443, $\eta^2_{partial}$ = .015), nor were the main effects for Temporal structure ($F_{(1, 40)}$ = 1.48; p = .232, $\eta^2_{partial}$ = .036), Formal structure ($F_{(1, 40)}$ = 2.43; p = .127, $\eta^2_{partial}$ = .057), Hemisphere ($F_{(2, 80)}$ = 1.48; p = .234, $\eta^2_{partial}$ = .036) or Region ($F_{(1, 40)}$ = .29; p = .681, $\eta^2_{partial}$ = .007) significant. Local latency measures of the P50 showed a three-way interaction between Deviance, Hemisphere and Group ($F_{(2, 80)}$ = 3.46; p = .039, $\eta^2_{partial}$ = .080). In addition there was a Timing by Region interaction ($F_{(2, 80)}$ = 3.89; p = .037, $\eta^2_{partial}$ = .089). Post-hoc analyses showed significantly delayed local peak latencies for deviant tones across medial regions compared to standard tones in the younger group ($t_{(20)}$ = 4.14, p = .001). For the left ($t_{(20)}$ = .83, p = .417) and right ($t_{(20)}$ = .33, p = .745) regions, the effect of deviance was not significant in the younger group. In the older group, none of the deviance effects were significant for the three regions. Post-hoc tests for the timing by region interaction indicated a significant effect of Temporal structure in parietal regions ($t_{(41)}$ = 2.52, p = .016), across groups. Moreover, when performing a one-sample t-test against zero in the younger group, the results indicated that there was indeed a significant effect for the P50 peak (all p-values were below $p < .000$).

N100

Results for the local mean amplitudes of the N100 component and topographical maps are presented in **Figure 3** for younger **(Figure 3A)** and older adults **(Figure 3B)**. Although the main effects of Group ($F_{(1, 40)}$ = .25; p = .618, $\eta^2_{partial}$ = .006) and Temporal structure ($F_{(1, 40)}$ = .46; p = .503, $\eta^2_{partial}$ = .011) were not significant, the main effects of Formal structure ($F_{(1, 40)}$ = 67.91; $p < .001$, $\eta^2_{partial}$ = .629), Hemisphere ($F_{(2, 80)}$ = 119.203; $p < .001$, $\eta^2_{partial}$ = .749) and Region ($F_{(2, 80)}$ = 57.73; $p < .001$, $\eta^2_{partial}$ = .591) were significant and further qualified by multiple interactions, including a significant interaction between all five factors ($F_{(4, 160)}$ = 4.42; p = .002, $\eta^2_{partial}$ = .099). As we expected the N100 to be most prominently displayed in fronto-central regions (Luck, 2014), post-hoc analyses for the medial-anterior ROI were performed. Results indicated more negative amplitudes for deviant tones (M = -1.46 μV) in comparison to standard tones (M = -1.03 μV) in the isochronous ($t_{(20)}$ = -4.69, $p < .001$) and more negative amplitudes for deviant (M = -1.61 μV) as opposed to standard tones (M = -1.14 μV) in the random sequence in younger adults ($t_{(20)}$ = -3.98, $p < .001$). Similar results were observed in the older group, more negative amplitudes for deviant tones (M = -1.48 μV) as compared to standard tones (M = -1.2 μV) in the isochronous ($t_{(20)}$ = -4.52, $p < .001$) and more negative amplitudes for deviant tones (M = -1.57 μV) as opposed to standard tones (M = -1.33 μV) in the random ($t_{(20)}$ = -3.15, p = .005) sequence. The differences between isochronous and random

conditions were not significant in younger (deviant: $t_{(20)}$ = 1.77, p = 0.092; standard: $t_{(20)}$ = 1.63, p = .119) and older (deviant: $t_{(20)}$ = 1.25, p = 0.226; standard: $t_{(20)}$ = 2.34, p = .12; Bonferroni corrected) adults.

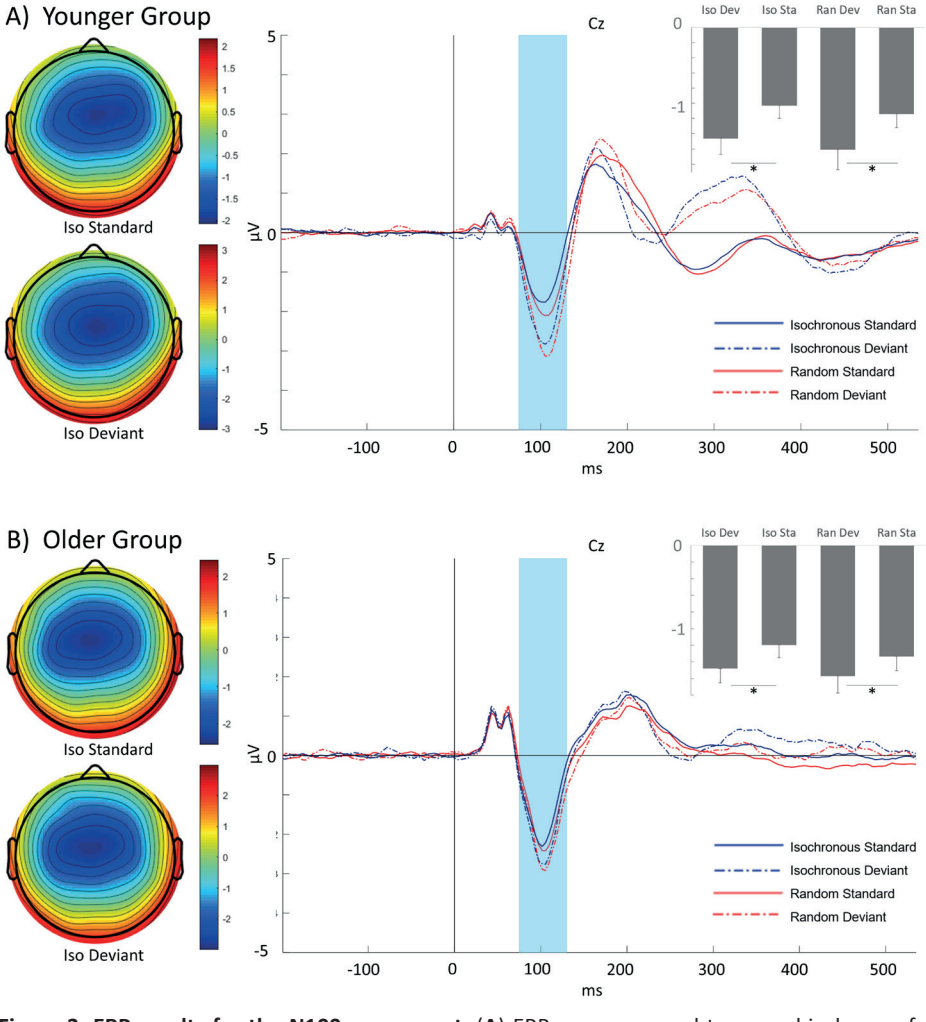

Figure 3. ERP results for the N100 component. (**A**) ERP responses and topographical maps for deviant and standard tones in the isochronous or random sequence for the younger and (**B**) older adult group. The bar plot reflects local mean amplitudes of the medial-anterior ROI.

Analyses of the local peak latency measures showed main effects for Group ($F_{(1, 40)}$ = 7.59; p = .009, $\eta^2_{partial}$ = .159) and Deviance ($F_{(1, 40)}$ = 20.06; p < .001, $\eta^2_{partial}$ = .334), reflecting overall delayed latencies in the older group (M = 101.14 ms, M younger group = 99.34 ms) and overall delayed latencies for deviant tones (M = 101.09 ms, M standard

tones = 99.39 ms). There were significant interactions between Region and Group ($F_{(2, 80)}$ = 14.98; $p < .001$, $\eta^2_{partial}$ = .272), and Timing and Hemisphere ($F_{(2, 80)}$ = 6.2; p = .003, $\eta^2_{partial}$ = .134). Post-hoc analyses across groups indicated an effect of Temporal structure in the medial ($t_{(41)}$ = -3.82, $p < .001$) and right ($t_{(41)}$ = 2.58, p = .014) regions, but not in the left ($t_{(41)}$ = .92, p = .36) regions. Post-hoc analyses on Region indicated significant latency differences between groups in the anterior ($t_{(40)}$ = -3.72, p = .001) and parietal region ($t_{(40)}$ = -3.94, $p < .001$), reflecting delayed latencies for the former in younger and delayed latencies for the latter in the older group.

P200

Results for the P200 component and topographical maps are presented in **Figure 4** for younger **(Figure 4A)** and older adults **(Figure 4B)**. While the main effect of Group ($F_{(1, 40)}$ = 2.52; p = .121, $\eta^2_{partial}$ = .059) and Temporal structure ($F_{(1, 40)}$ = .519; p = .475, $\eta^2_{partial}$ = .013) were not significant, the main effects of Formal structure ($F_{(1, 40)}$ = 5.57; p = .026, $\eta^2_{partial}$ = .118), Hemisphere ($F_{(2, 80)}$ = 56.63; $p < .001$, $\eta^2_{partial}$ = .586) and Region ($F_{(2, 80)}$ = 16.4; $p < .001$, $\eta^2_{partial}$ = .291) were significant and further qualified by multiple interactions, including a significant interaction between all five factors ($F_{(4, 160)}$ = 2.78; p = .038, $\eta^2_{partial}$ = .065). We expected the P200 to be most prominently displayed in fronto-central regions (Luck, 2014). Post-hoc analyses of the medial-anterior ROI showed a marginally significant effect of Temporal structure (i.e., increased amplitudes for the random sequence (M = .7 µV) as opposed to the isochronous sequence, M = .48 µV) for standard tones in the younger group ($t_{(20)}$ = -2.68, p = .056; Bonferroni corrected). The effect of Temporal structure for deviant tones was not significant in the younger group ($t_{(20)}$ = -2.14, p = .09; Bonferroni corrected). Similarly, in the older group, the effect of Temporal structure for deviant tones was also not significant ($t_{(20)}$ = 2.59, p = .072; Bonferroni corrected). For the Temporal structure, for standard tones, there was a difference between isochronous and random sequences ($t_{(20)}$ = 3.56, p = .002), suggesting increased amplitudes for standard tones (M = .96 µV) in the isochronous sequence as opposed to standard tones in the random sequence (M = .68 µV) in the older group. The effects for Formal structure were not significant in the younger (isochronous: $t_{(20)}$ = -1.49, p = .153; random: ($t_{(20)}$ = -1.03, p = .315) and older group (isochronous: $t_{(20)}$ = -1.93, p = .069; random: ($t_{(20)}$ = -2.29, p = .132), after Bonferroni correction.

Although analyses of the local peak latencies for the P200 indicated non-significant main effects for Temporal structure ($F_{(1, 40)}$ = 2.37; p = .131, $\eta^2_{partial}$ = .056) and Formal structure ($F_{(1, 40)}$ = 1.64; p = .208, $\eta^2_{partial}$ = .039), the main effects of Group ($F_{(1, 40)}$ = 5.04; p = .030, $\eta^2_{partial}$ = .112), Hemisphere ($F_{(2, 80)}$ = 14.24; $p < .001$, $\eta^2_{partial}$ = .262)

and Region ($F_{(2, 80)}$ = 13.29; p < .001, $\eta^2_{partial}$ = .249) were significant and further qualified by a significant five-way interaction between all factors ($F_{(1, 40)}$ = 5.04; p = .030, $\eta^2_{partial}$ = .112). As we expected the P200 to be most prominently displayed in fronto-central regions (Luck, 2014), post-hoc analyses of the medial-anterior ROI were performed and displayed a significant effect of Temporal structure for deviant tones in the younger group ($t_{(20)}$ = -4.58, p < .001), indicating delayed latencies in the random condition (M = 175.5 ms) as opposed to the isochronous ones (M = 168.56 ms). The same effect was not significant in the older group ($t_{(20)}$ = -1.48, p = .15).

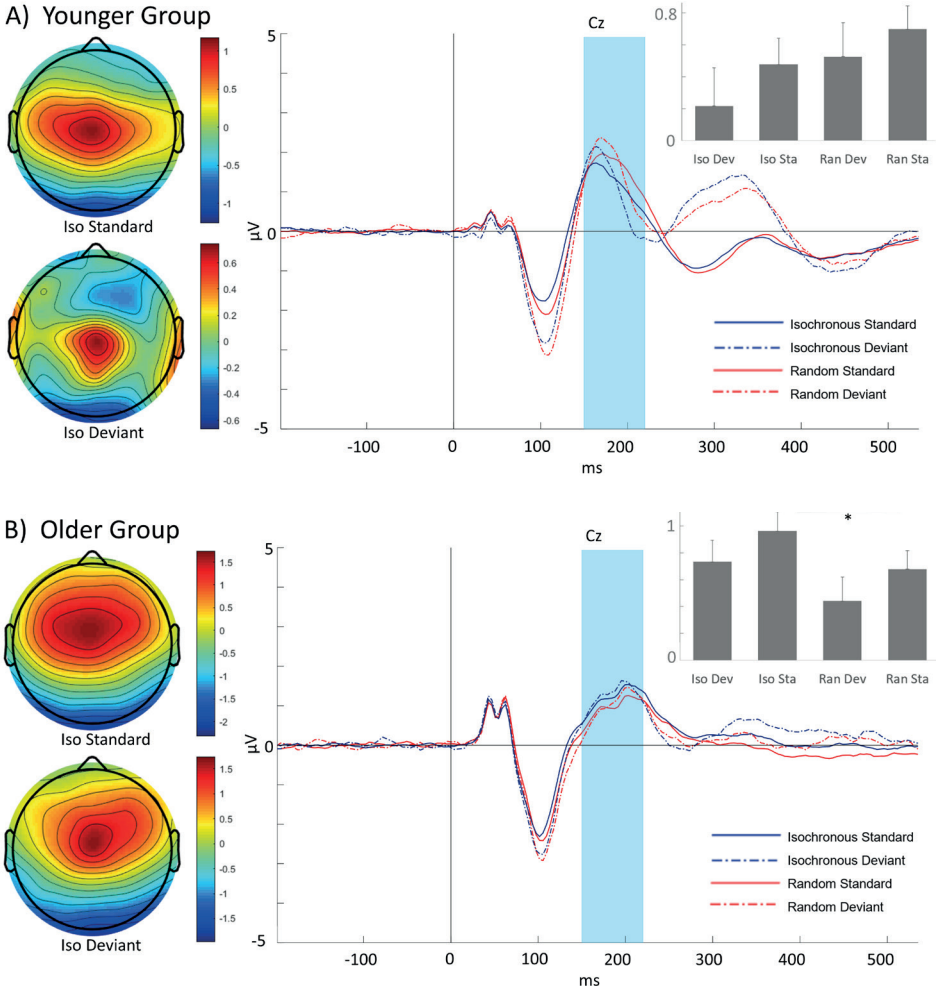

Figure 4. ERP results for the P200 component. ERP responses and topographical maps for deviant and standard tones in the isochronous or random sequence for the (**A**) younger and (**B**) older adult group. The bar plot reflects local mean amplitudes of the medial-anterior ROI.

The effect of Temporal structure for standard tones was not significant in the younger group ($t_{(20)}$ = -.11, p = .915), similar to the same effect in the older group ($t_{(20)}$ = .18, p = .86). The effects of Formal structure were not significant in the younger (isochronous: $t_{(20)}$ = -1.76, p = .093; random: $t_{(20)}$ = -.08, p = .941) and older group (isochronous: $t_{(20)}$ = -1.32, p = .201; random: $t_{(20)}$ = -.24, p = .815). For older adults, the latencies were increasingly delayed in anterior (M = 192.8 ms) as opposed to central (M = 187.6 ms) or parietal regions (M = 173.4 ms).

P300

Results with respect to the P300 component and topographical maps are presented in **Figure 5** for younger **(Figure 5A)** and older adults **(Figure 5B)**. The main effects of Group ($F_{(1, 40)}$ = 4.57; p = .039, $\eta^2_{partial}$ = .102), Temporal structure ($F_{(1, 40)}$ = 17.82; $p < .001$, $\eta^2_{partial}$ = .308), Formal structure ($F_{(1, 40)}$ = 51.36; $p < .001$, $\eta^2_{partial}$ = .562), Hemisphere ($F_{(2, 80)}$ = 4.25; p = .020, $\eta^2_{partial}$ = .096) and Region ($F_{(2, 80)}$ = 16.26; $p < .001$, $\eta^2_{partial}$ = .289) were significant and further qualified by multiple interactions. The analyses of the local mean amplitude for the P300 yielded a significant interaction between Formal structure, Hemisphere, Region and Group ($F_{(4, 160)}$ = 3.31; p = .020, $\eta^2_{partial}$ = .076), between Temporal structure, Region and Group ($F_{(2, 80)}$ = 4.49; p = .033, $\eta^2_{partial}$ = .101) and between Temporal structure, Hemisphere and Group ($F_{(2, 80)}$ = 3.32; p = .045, $\eta^2_{partial}$ = .077). Post-hoc comparisons for the Formal structure, Hemisphere, Region and Group interaction showed significant effects for Formal structure for the medial-central ($t_{(20)}$ = 4.87, $p < .001$), medial-parietal ($t_{(20)}$ = 5.6, $p < .001$), right-anterior ($t_{(20)}$ = -3.89, p = .001) and left-anterior ($t_{(20)}$ = -3.46, p = .003) ROIs in the younger group. For the older group significant effects of formal structure for the medial-anterior ($t_{(20)}$ = 3.34, p = .003), right-anterior ($t_{(20)}$ = 4.28, $p < .001$), left-central ($t_{(20)}$ = -3.5, p = .002), left-parietal ($t_{(20)}$ = -3.96, p = .001), and right-parietal ($t_{(20)}$ = -3.35, p = .003) ROIs were observed. Post-hoc analyses for the Temporal structure, Region and Group indicated an effect for Temporal structure in the in the central region in the younger group ($t_{(20)}$ = 2.71, p = .013), but not in the anterior ($t_{(20)}$ = -1.8, p = .087) or parietal ($t_{(20)}$ = 1.6, p = .127) region. In the older group, none of the regions showed a significant effect of temporal structure (anterior: $t_{(20)}$ = 1.45, p = .162; central: $t_{(20)}$ = 1.84, p = .08; parietal: $t_{(20)}$ = -1.33, p = .202). Post-hoc analyses on the Temporal structure, Hemisphere and Group yielded significantly increased amplitudes in the isochronous condition as compared to the random condition in the older group in medial areas ($t_{(20)}$ = 3.2, p = .005), but not in left ($t_{(20)}$ = -2.39, p = .081) or right ($t_{(20)}$ = -.19, p = .85) areas. In the younger group, none of the effects were significant (left: $t_{(20)}$ = -.16, p = .872; medial: $t_{(20)}$ = .65, p = .53; right: $t_{(20)}$ = 1.4, p = .17). There was a significant Hemisphere by Group ($F_{(2, 80)}$ = 5.54; p = .007, $\eta^2_{partial}$ = .122) and Region by Group interaction ($F_{(2, 80)}$ = 38.4; $p < .001$, $\eta^2_{partial}$ = .490), indicating

hemispheric differences only when comparing medial to right areas in the younger group ($t_{(20)}$ = -3.44, p = .003), while the differences between left and medial ($t_{(20)}$ = 2.44, p = .072; Bonferroni corrected), and left and right ($t_{(20)}$ = -1.28, p = .216) were not significant. In the older group, none of the comparisons were significant (left vs medial: $t_{(20)}$ = -2.17, p = .126 ;medial vs right: $t_{(20)}$ = -.07, p = .944; left vs right: $t_{(20)}$ = -2.51, p = .063; Bonferroni corrected). For the Region by Group interaction, significant differences were observed between anterior and parietal regions in both groups (younger: $t_{(20)}$ = -6.16, $p < .001$; older: $t_{(20)}$ = 2.75, p = .012), between central and parietal regions in both groups (younger: $t_{(20)}$ = -3.98, p = .001; older: $t_{(20)}$ = 2.86, p = .010) and between anterior and central regions only in the younger ($t_{(20)}$ = -5.58, $p < .001$), but not in the older group ($t_{(20)}$ = 1.49, p = .153). These effects for Region showed overall increased amplitudes for anterior regions in older and increased amplitudes for parietal regions in younger adults.

Local peak latency analyses showed main effects of Group ($F_{(1, 40)}$ = 14.6; $p < .001$, $\eta^2_{partial}$ = .267), Formal structure ($F_{(1, 40)}$ = 4.15; p = .048, $\eta^2_{partial}$ = .094) and Region ($F_{(2, 80)}$ = 14.6; $p < .001$, $\eta^2_{partial}$ = .251), but not Temporal structure ($F_{(1, 40)}$ = .167; p = .685, $\eta^2_{partial}$ = .004) and Hemisphere ($F_{(2, 80)}$ = 3.03; p = .062, $\eta^2_{partial}$ = .07), which were further qualified by multiple interactions. There was a significant interaction between Formal structure, Region and Group ($F_{(2, 80)}$ = 15.26; $p < .001$, $\eta^2_{partial}$ = .276), in addition to an interaction between Formal structure, Hemisphere and Group ($F_{(2, 80)}$ = 23.24; $p < .001$, $\eta^2_{partial}$ = .367). Post-hoc analyses in the younger group showed significant effects for Formal structure in the anterior ($t_{(20)}$ = 3.46, p = .002) and the parietal ($t_{(20)}$ = -4.32, $p < .001$), but not central ROIs ($t_{(20)}$ = 2.54, p = .06; Bonferroni corrected). In the older group, the difference between standard and deviant tones was significant for anterior and central but not parietal areas (anterior: $t_{(20)}$ = -3.0, p = .007; central: $t_{(20)}$ = -2.76, p = .012; parietal: $t_{(20)}$ = -.39, p = .699). Post-hoc tests for the Formal structure, Hemisphere and Group interaction, revealed an effect of Formal structure in the medial ($t_{(20)}$ = 3.7, p = .001), but not left ($t_{(20)}$ = -2.22, p = .114; Bonferroni corrected) and right ($t_{(20)}$ = -1.54, p = .139) areas for younger adults. Similar results were observed for older adults for the medial ($t_{(20)}$ = -5.1, p = .000), left ($t_{(20)}$ = .48, p = .636) and right ($t_{(20)}$ = -.98, p = .341) areas. The significant Region by Group interaction ($F_{(1, 40)}$ = 42.2; $p < .001$, $\eta^2_{partial}$ = .513) indicated significant differences between anterior and central ($t_{(20)}$ = -5.18, $p < .001$), central and parietal ($t_{(20)}$ = -9.43, $p < .001$) and anterior and parietal ($t_{(20)}$ = -9.64, $p < .001$) regions in the older group, but not in the younger group (anterior vs central: $t_{(20)}$ = 1.02, p = .321; central vs parietal: $t_{(20)}$ = -1.87, p = .076; anterior vs parietal: $t_{(20)}$ = 1.96, p = .064), suggesting delayed latencies in parietal regions (M = 436.63 ms) as compared to central (M = 372.1 ms) and anterior (M = 334.7 ms) regions in older adults.

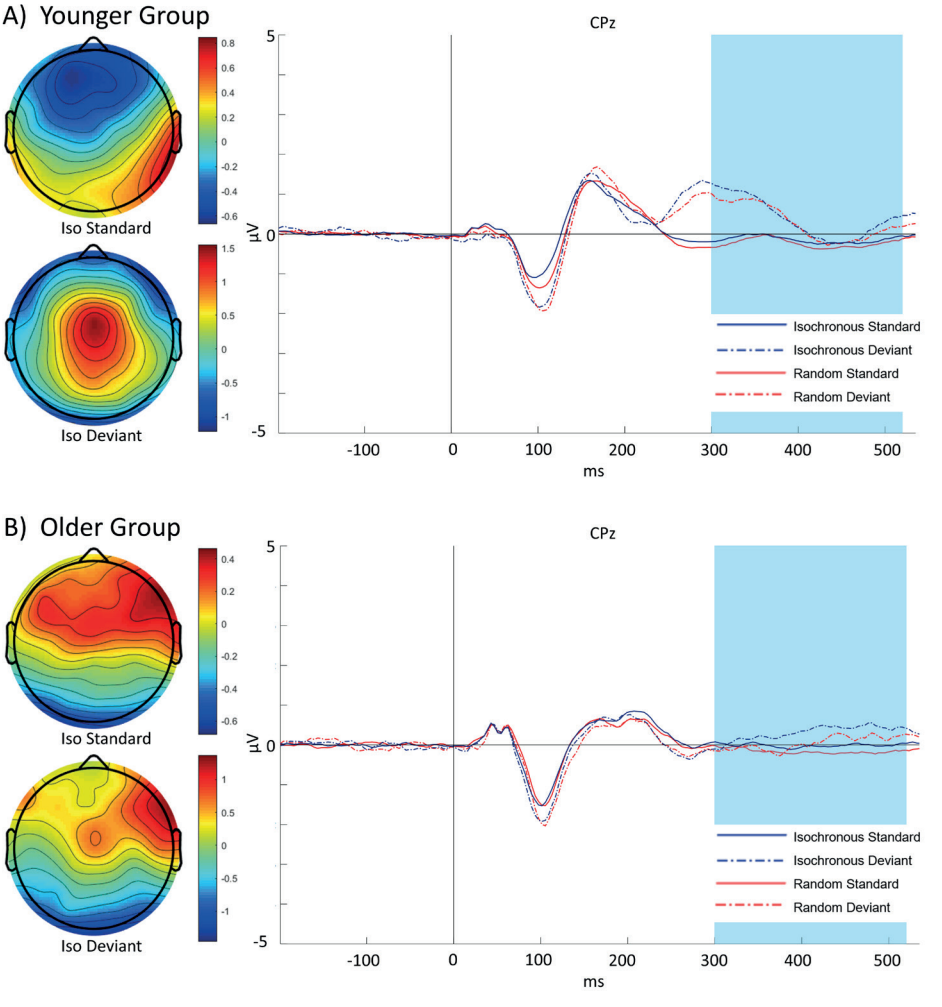

Figure 5. ERP results for the P300 component. ERP responses and topographical maps for deviant and standard tones in the isochronous or random sequence for (**A**) younger adults and (**B**) older adults at 330ms.

In sum, the overall pattern of results indicated an influence of age on P50 amplitude, N100, P200 and P300 latencies. The findings showed that older adults display overall enhanced P50 amplitudes and delayed latencies for N100 P200 and P300. Post-hoc tests showed a difference between isochronous and random sequences in the younger, but not in the older group for the P50. For the P50 latency, the effect of Temporal structure was visible in parietal regions. For the N100, younger and older adults displayed more negative amplitudes for deviant tones. For the P200, marginally significant amplitude reductions for the isochronous sequences were observed for standard tones in younger

and increased amplitudes for standard tones in the isochronous sequence as compared to the random sequence in older adults. For the P200 latency, delayed latencies for the deviant tones in the isochronous sequence were observed in younger, but not in older adults. Lastly, for the P300 latencies, stimuli were processed earlier in anterior ROIs, followed by central ROIs and parietal ROIs in the older group. For the P300 latencies the younger group, stimuli were generally processed earlier in parietal, then in central and then anterior regions.

Discussion

The goal of the current study was to examine the effect of age on the neural signatures of temporal predictability in auditory sequences. Although several studies investigated the influence of age on timing capacities, few focused on ERP signatures of temporal predictability, while independently manipulating formal and temporal structure. In the present study, younger and older adults were tested, and neural activity was recorded in a classic oddball paradigm. We observed differential neural signatures for temporal predictability for younger and older adults. Compared to younger participants, older adults displayed an overall increased P50 amplitude, followed by delayed N100, P200, P300 latencies in response to the manipulation of temporal and formal structure. More specifically, temporal predictability (i.e., isochronous versus random auditory sequences) interacted with age, as altered P50 amplitudes were observed in younger but not older adults. This suggests early differentiation of evoked responses between the two groups. Below, we will discuss these patterns of results in more detail.

The Global Effect of Age and the Effects of Age on Temporal and Formal structure

Based on previous studies, we expected specific age effects on the ERP components of interest (Golob et al., 2007; Nowak et al., 2016). Our findings are generally in line with these expectations, as the results confirmed main effects of age for changes in P50 amplitude and N100, P200 and P300 latencies. The increased P50 response to temporally predictable and random tone sequences is in line with reduced sensory gating in the older group. Previously, with increased age, sensory gating was found to be decreased, as indicated by reduced paired-stimulus suppression of the P50 (Patterson et al., 2008). In turn, reduced sensory gating might be linked to less efficient inhibitory processing, considering that the P50 is at least partly generated in the frontal lobes that regulate cognitive control (Korzyukov et al., 2007; Miller, 2000). Similar results were obtained in the context of pathologic ageing, indicating a P50 amplitude increase in patients

with Alzheimer's disease (Green et al., 2015; Morrison, Rabipour, Knoefel, Sheppard, & Taler, 2018). Although the current study focused on healthy ageing, evidence from these studies suggests that sensitivity differences observed in younger and older adults may be underpinned by similar mechanisms, thus they might possibly be of quantitative nature. Moreover, the P200 and P300 peak latencies were globally delayed for deviant tones in older adults, an effect which was also found by Golob et al. (2007). It has been suggested that the P300 may serve as an index of cognitive ageing, where P300 latencies may reflect neural speed and P300 amplitudes neural power (van Dinteren, Arns, Jongsma, & Kessels, 2014). Moreover, an overall decreased P300 amplitude was observed in the elderly group. Hence, our results are generally in line with previous findings, where with increasing age, P300 target amplitudes decreased and latencies increased (Bourisly, 2016; Fjell & Walhovd, 2001; van Dinteren et al., 2014).

We expected to find interactions of ERP amplitudes and latencies by formal and temporal structure, per age group. Firstly, following the manipulation of temporal structure (i.e., isochronous versus random auditory sequences) the P50 amplitude differed between isochronous and random sequences in the younger adult group, but not in the elderly. This effect of temporal structure in younger participants could also be linked to sensory gating, suggesting less efficient temporal sensory gating for random sequences, in comparison to temporal regular ones. Therefore, the results support the role of the P50 as a marker for temporal predictability only for younger adults (Schwartze et al., 2013), while they highlight less efficient inhibitory processing for older adults. For the P200, increases in amplitude for the isochronous sequence as opposed to the random sequence were observed for standard tones in older but not in younger adults. This could also be interpreted as support for less efficient sensory gating in the elderly for isochronous sequences. Previously, similar findings were observed when investigating pitch discrimination with different foreperiods, thus manipulating temporal predictability (Herbst & Obleser, 2017).

Secondly, effects related to formal structure (i.e., standard versus deviant tones) per age group were more complex than for temporal structure in the P50 and N100 components. For the P50 latency, the processing of standard and deviant tones in the younger group differed significantly, while this was not the case in the older group. Moreover, N100 amplitude values indicated differences in formal structure in both groups similarly to reports by Schwartze, Rothermich, et al. (2011). This suggests that formal structure similarly influences the mean N100 amplitude in both groups, while formal structure is distinguishable between groups regarding the P50 latency. Also, the previously mentioned P300 interactions indicate an expected response to deviance in the younger and in the

older group but at different ROIs, but in anterior and parietal regions for both groups. Deviants across isochronous and random contexts exhibited larger responses in the younger as opposed to the older group, which is again, in line with the known literature (Bourisly, 2016; Fjell & Walhovd, 2001; van Dinteren et al., 2014).

Moreover, the anteriorisation of the P300 was shown in shortened latencies in anterior regions as compared to parietal regions in the older group. In addition, increased amplitudes for anterior regions were found in older adults and increased amplitudes for parietal regions in younger adults for P300 amplitudes. The anteriorisation of the P300 is a well-known effect occurring when ageing (Fallgatter, Mueller, & Strik, 1999).

To summarize, our results suggest an effect of age for P300 latency and differential processing mechanisms for the P300 amplitude responses when comparing younger with older adults. Regarding temporal structure, our results suggest differential processing mechanisms for P50 amplitude, in addition to the overall age-related amplitude increases for P50 and latency delays for N100, P200 and P300.

Conclusion

The present study highlights age effects on neural correlates of temporal and formal predictability. These findings provide robust evidence in support of our hypothesis that the P50 may serve as a marker of temporal predictability in younger adults. Our results further suggest that P200 amplitudes increased for the isochronous sequence as opposed to the random sequence for standard tones in older adults, while the opposite pattern was observed in younger adults. In conclusion, temporal sensory gating was less efficient in the elderly group. This could in turn influence predictive adaptation behavior in the ageing population, which is based on extracting temporally predictable events in our environment. Thus, processing the information transmitted by the initial example of the parking assistant might underlie different or less sensitive temporal predictability mechanisms in younger and older adults. To underline the importance of our results also with respect to pathological ageing, this study may serve as first step to establish a baseline, when investigating patients with neurodegenerative diseases. One may speculate that patients diagnosed with Alzheimer's or Parkinson's disease display an even increased temporal sensory gating impairment.

Future studies, examining age effects for neural signatures of temporal predictability, should try to disentangle whether the observed age-related differences for temporal structure are based on quantitative or qualitative nature (i.e., the same mechanism, but less sensitive or two different kinds of mechanisms).


4

Chapter 4

Parallel EEG assessment of different sound predictability levels in tinnitus

Brinkmann, P., *Devos, J. V., van der Eerden, J. H., Smit, J. V., Janssen, M. L., Kotz, S. A., & Schwartze, M. (2023). Parallel EEG assessment of different sound predictability levels in tinnitus. bioRxiv, 2023-07.*

Under review

Abstract

Objective: Tinnitus denotes perception of a non-environmental sound and might result from aberrant auditory prediction. Successful prediction of formal (e.g., type) and temporal sound characteristics facilitates the filtering of irrelevant information ("sensory gating", SG). Here, we explored if and how parallel manipulations of formal and temporal predictability affect sensory gating in persons with and without tinnitus.

Methods: Age-, education- and sex-matched persons with and without tinnitus (N = 52) participated and listened to paired-tone "oddball" sequences, varying in formal (standard vs. deviant pitch) and temporal predictability (isochronous vs. random timing). EEG was recorded from 128 channels and data were analyzed by means of temporal spatial principal component analysis (tsPCA).

Results: SG was observed in P50- and N100-like activity (amplitude suppression for the 2nd tone in the pair) in both timing conditions and groups. Correspondingly, deviants elicited overall larger amplitudes than standards. However, only in persons without tinnitus N100-like activity in response to deviants was enhanced with isochronous relative to random timing.

Conclusions: Persons with tinnitus do not benefit similarly as persons without tinnitus from temporally predictable context in deviance processing.

Significance: The current results indicate altered temporal sensitivity and selective attention allocation in persons with tinnitus.

Introduction

Predicting the type and timing of upcoming events guides goal-directed behavior and is key to efficiently adapting to changes in an abundant sensory environment. In audition, predictions can take different forms. They are either based on formal (type) or temporal (timing) stimulus characteristics (Bendixen et al., 2012; Mauk & Buonomano, 2004; Tavano, Widmann, Bendixen, Trujillo-Barreto, & Schröger, 2014). Formal predictions refer to the spectral information that is conveyed in an acoustic stimulus (Schwartze et al., 2012), while temporal predictions refer to the points in time when a stimulus event occurs (Schwartze et al., 2012). Nested in this basic distinction, predictions can be based on specific stimulus arrangements such as the repetitive binary stimulus grouping that is commonly used in 'sensory gating' (SG) studies to induce position predictions.

The fundamental importance of predictions is particularly evident when their underlying mechanisms change in pathological conditions. One condition in which altered auditory predictions seem to play a role is tinnitus (Brinkmann, Kotz, Smit, Janssen, & Schwartze, 2021; De Ridder et al., 2014; Hullfish et al., 2019; Roberts, Husain, & Eggermont, 2013; Sedley et al., 2016). Tinnitus is typically described as the 'ringing in the ears' and often experienced as a constant sound in the absence of any physical sound source (Axelsson & Ringdahl, 1989; Roberts et al., 2010). The most prominent risk factors for developing tinnitus are aging and hearing loss (Roberts et al., 2010). In the general population, its prevalence ranges from 10-14% in middle-aged adults and further increases with age (Jarach et al., 2022; Langguth et al., 2013). Persons with tinnitus are either characterized by decompensated or compensated tinnitus. The first group suffers from tinnitus while the second is not substantially affected by it.

Taking a predictive coding perspective, chronic tinnitus might display altered default predictions, meaning that in chronic tinnitus, default predictions in audition change to represent 'something' instead of 'silence' (Hullfish et al., 2019; Sedley et al., 2019). Alternatively, peripheral or subcortical tinnitus models propose that tinnitus might stem from aberrant cochlear activity (Mulders & Robertson, 2009) or impaired noise-cancellation due to malfunctioning in limbic structures (Rauschecker et al., 2010). It was suggested that tinnitus results from discrepant expected and actual auditory input in interaction with attention (Roberts et al., 2013). Although the exact interplay of these factors is unknown, discrepancy of this kind can lead to auditory phantom perception. As tinnitus is typically perceived as a tone with a constant pitch, it is assumed that formal predictions are most affected (Sedley et al., 2019). Additionally, altered temporal predictions in tinnitus have first been suggested in thalamocortical dysrhythmia (De

Ridder et al., 2015) and were subsequently discussed in a predictive network hypothesis (Brinkmann et al., 2021). Accordingly, distinguishing dimensions of auditory prediction (i.e., formal-, temporal-, and position-predictions) combined with a differential assessment of their function in tinnitus might lead to a better and more comprehensive understanding of tinnitus beyond the level of formal predictions.

The high temporal resolution of the electroencephalogram (EEG) provides an excellent tool for investigating auditory predictions. The P50 and N100 event-related potential components (ERPs) that peak around 50 and 100 ms post-stimulus respectively are responsive to prediction. SG is often described as a predictive filtering mechanism and investigated by presenting pairs of identical sound stimuli. The response to the second stimulus leads to a suppressed P50 ERP response (i.e., 'gating out'), and indicates that the first stimulus is predictive of the second one (Adler et al., 1982; Cromwell et al., 2008).

The P50 is generated in temporal and frontal cortices and interpreted as an indicator of SG (Korzyukov et al., 2007; Smith et al., 1994). P50 SG is conceived as a pre-attentional mechanism and mainly reflects sensory processes (Jerger, Biggins, & Fein, 1992; Kho et al., 2003). Modulation of the P50 response in SG might thus indicate the relative success of filtering out goal-irrelevant information (Jones, Hills, Dick, Jones, & Bright, 2016). Accordingly, stronger P50 suppression is associated with better attentional orienting and inhibition (Wan, Friedman, Boutros, & Crawford, 2008).

The N100 is generated in the supratemporal plane of the auditory cortex (Näätänen & Picton, 1987) but also in the frontal cortex (Giard et al., 1994). The N100 reliably indicates formal predictions as assessed in pitch-based "oddball" paradigms (Segalowitz & Barnes, 1993) and stands more for (selective) attentional processes (Thornton, Harmer, & Lavoie, 2007). Previous N100 research, that manipulated formal and temporal stimulus predictability, found differences between temporal and formal conditions (Schwartze et al., 2013). The N100 response to predictable stimuli becomes smaller over time and the interval between the stimuli is a factor that determines this decrease (Budd, Barry, Gordon, Rennie, & Michie, 1998). Taken together, the existing evidence suggests that the P50 and N100 might indicate different stages of predictive sensory filtering, with successful SG leading to better task performance and protected higher-order cognitive functioning (Lijffijt et al., 2009; Venables, 1964).

Neurophysiological SG studies in adults with tinnitus have produced inconclusive results (Campbell et al., 2018; Dornhoffer, Danner, Mennemeier, Blake, & Garcia-Rill, 2006).

For example, it has been shown that the SG difference index of the Pa component that precedes the P50, correlates negatively with tinnitus severity, i.e., more severe tinnitus reduced the Pa suppression in response to the second tone in a tone pair (Campbell et al., 2018). However, no significant differences were observed between persons with tinnitus and those without for Pa, P50, N100 or P200 gating effects (Campbell et al., 2018). Notably, participants in this study only experienced mild tinnitus symptoms as assessed by the tinnitus handicap inventory (THI) (Newman, Jacobson, & Spitzer, 1996). Another study investigated P50 suppression in persons with and without tinnitus and similarly did not report group differences (Dornhoffer et al., 2006). Habituation to repetitive auditory input seems to be reduced in persons with decompensated tinnitus as evident in N100 and P200 amplitude differences (Walpurger, Hebing-Lennartz, Denecke, & Pietrowsky, 2003). Sedley et al. (2019) manipulated formal predictability in a roving standard oddball paradigm and observed no differences between persons with or without tinnitus comparing their response to standard and deviant tones in the P50, while deviants evoked larger N100 responses in both groups. Thus, previous evidence shows reduced N100 - P200 amplitude differences during continuous repetitive stimulus presentation in persons with decompensated tinnitus (Walpurger et al., 2003), that increased tinnitus burden might be linked to impaired Pa suppression (Campbell et al., 2018), while for P50 SG no group differences were found (Dornhoffer et al., 2006). Research focusing on P50 and N100 responses as indices for stimulus type or temporal predictability in tinnitus thus likely reflect the heterogeneity of the condition (Cederroth et al., 2019).

Tinnitus has previously been investigated by means of stimulus sequences that incorporated manipulations of either formal or position prediction in isolation (Campbell et al., 2018; Dornhoffer et al., 2006; Sedley et al., 2019). However, experimental paradigms that allow the parallel assessment of different stimulus type dimensions and timing are needed to obtain a better understanding of how prediction impacts tinnitus heterogeneity. Such a comprehensive approach could allow differentiating individual prediction capacities and identify which dimensions are dysfunctional in tinnitus. As SG is a filtering mechanism that might operate on all predictability dimensions, it also allows exploring possible interactions between temporal-, formal- and position-based SG. Finally, linking this approach to specific ERP markers, such as P50 and N100, might allow decomposing the underlying mechanisms of selective attention and inform how they look in persons suffering from tinnitus.

Along these lines, the current study assessed if and how ERP markers of auditory predictions are altered in persons with and without tinnitus. The experimental setup incorporated a paired-tone oddball design that simultaneously manipulated formal and temporal stimulus features to differentiate and relate different aspects of predictability. This setup combined elements of previous studies (Schwartze et al., 2013; Schwartze, Rothermich, et al., 2011) with the aim to verify if previous findings could be reproduced. It was expected that tinnitus alters SG efficiency. Accordingly, it was hypothesized that successful SG for position, deviance, and regularity dimensions would result in smaller P50 and N100 amplitudes for predictable stimuli but that dysfunctional SG in tinnitus would lead to increased P50 and N100 amplitudes.

Methods

The study was approved by the ethics committee of the Maastricht University Medical Center + (MUMC+) with the code 2019-0970. Due to the COVID pandemic, data collection was paused and then continued intermittently under strict safety regulations.

Recruitment and inclusion

Participants were recruited via leaflets, word of mouth, and an existing database of persons with tinnitus. Persons with and without (subjective) tinnitus were included when they were between 18 and 69 years old and had an audiogram and a bilateral high tone Fletcher Index lower than 60 dB. Exclusion criteria were objective tinnitus (i.e., pulsatile tinnitus), a maximum air-bone gap of more than 20 dB, or a history of ear surgery, brain surgery or brain/ear implants. If available, participants provided their audiograms, all but seven obtained within the last year, otherwise an audiogram was obtained by trained personnel before testing. The two groups were matched for sex at the participant level and for age and education at the group level.

Participants

Fifty-two persons with tinnitus and without participated (**Table 1**). Education was scored on 8 levels in persons with and without tinnitus, where 8 was the highest level. Handedness was assessed with the Dutch handedness questionnaire (van Strien, 2003) on a scale ranging from -10 (extreme left-handedness) to 10 (extreme right-handedness) for persons with tinnitus and without. Hearing loss (HL) was assessed using the average pure tone audiometry (PTA) in dB for the left and right ears for persons with tinnitus and without. Tinnitus burden was assessed with the Dutch version of the Tinnitus Questionnaire (TQ) (Goebel & Hiller, 1994; Meeus, Blaivie, & Van de

Heyning, 2007) in the tinnitus group (*MTQ* = 37.3, *SDTQ* = 17.6), scores between 31 and 46 points indicate mild tinnitus burden (Grade II). Tinnitus duration was assessed in months (*MTinDuration* = 82.8, *SDTinDuration* = 76.4). The tinnitus group suffered from chronic tinnitus, considering that tinnitus is 'chronic' if it is experienced for at least three months (Snow, 2004).

Table 1. **Demographics of the study participants.**

Variables	with Tinnitus	without Tinnitus
Total Number (n)	27 (7 female)	25 (6 female)
Age ± SD	50.6 ± 14.1	44.8 ± 16.3
Education (0-8)	4.5 ± 1.6	5.3 ± 1.7
Handedness (-10 – 10)	8.2 ± 3.7	4.6 ± 8.2
Pure tone average (PTA) in dB for both ears	23.2 ± 12.3	11.7 ± 12.9 **

** $p \leq .01$

Materials

Procedure

Upon arrival at the laboratory, participants signed the informed consent and performed the handedness questionnaire, answered questions about their tinnitus (i.e., tinnitus duration etc.), and filled in the TQ. They then entered an electronically shielded and soundproof booth for the EEG recordings.

Experimental design and stimuli

The two stimulus sequences each consisted of 1152 standard (600 Hz) and 288 deviant (660 Hz) tones (50 ms duration including 5 ms rise and fall times) corresponding to a 4:1 standard to deviant ratio. The total duration of each sequence was 12 min and participants were given a short break after 6 min. Alternating short and long intervals between tones ensured that the sequences resembled typical paired stimulus SG paradigms (**Figure 1**). The intervals between the tones of a pair (intra-pair-interval, intra-PI) were 200 ms in the fully predictable isochronous sequence and between 100-300 ms in the random sequence. The intervals between pairs (inter-pair-interval, inter-PI) were 700 ms in the isochronous sequence and between 350-1050 ms in the random sequence. The random sequence was designed so that participants still perceived the tones in pairs, but the intra-PIs (100ms, 150ms, 200 ms, 250 ms, 300 ms) and inter-PIs (350 ms, 525 ms, 700 ms, 875 ms, 1050 ms) varied. The order of these time intervals was randomized using a Williams design (Williams, 1949).

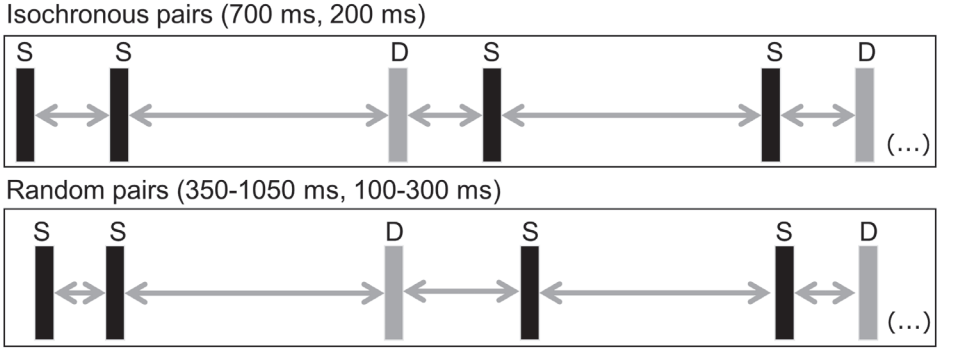

Figure 1. Schematic representation of the stimulus sequences. Pairs of sinusoidal tones were continuously presented in two sequences, one in which the intervals between tones and pairs were fixed (isochronous pairs) and one in which both intervals varied in duration with the constraint that shorter and longer intervals alternated (random pairs). Black bars represent standard tones (S), gray ones deviant tones (D). Standard and deviant tones differed in pitch and were presented with an overall 4:1 ratio.

EEG recording and pre-processing

EEG was recorded from 128 active electrodes (actiCAP, Brain Products GmbH), mounted into an elastic cap at 1000 Hz sampling rate, while impedances were kept at ≤10 kOhm. FCz was used as the online reference and the audio signal was recorded with the EEG. Data were then downsampled to 500 Hz and a bandpass filter (1-44 Hz) was applied using EEGlab (Delorme & Makeig, 2004). To detect and reject bad channels *clean_rawdata* was used (Mullen et al., 2015). Rejected channels (*M* = 5.5, *SD* = 4.9) were spherically interpolated, then the online reference was added back to the data and data were re-referenced to the average (following Foti et al. (2009)). Artifact subspace reconstruction (ASR) was performed using *clean_rawdata* and data were re-referenced again as suggested by Makoto (2022) to reorganize the data to be zero-sum across channels. Then ICA (runica; 30 pca components) was performed (Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997). IC components (*M* = 4.3, *SD* = 1.2) reflecting eye horizontal and vertical movements, muscle activity, heart rate, line noise or channel noise were rejected using *IClabel* (Pion-Tonachini, Kreutz-Delgado, & Makeig, 2019).

ERP analysis

Epochs lasting from -50 ms to 145 ms relative to stimulus onset were created, baseline corrected (-50 to 0 ms), and then averaged per participant. To avoid bias or double dipping about time and spatial distribution of the ERP components (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009; Luck & Gaspelin, 2017), analyses followed a data-

driven approach. A two-step temporal-spatial PCA (tsPCA) was performed using the EP toolkit (version 2.95) (Dien, 2010a; Dien, 2012). This procedure decomposes the data based on covariances between voltages at sampling points and sampling sites and aims to identify and disentangle components that are transparently and objectively extracted (Dien & Frishkoff, 2005). Following the guidelines formulated by Dien (2012), first, a temporal PCA was performed on the averaged data, using participants, stimulus types, and recording sites as observations. A (oblique) Promax rotation was used (Hendrickson & White, 1964) and seven factors were extracted after inspection of the scree plot (Cattell, 1966) with the help of a parallel test that compares the scree plot obtained with the experimental data with one that is derived from random data (Horn, 1965). Second, a spatial (orthogonal) Infomax ICA was performed on each temporal component that survived the first step, and seven spatial components were extracted (Bell & Sejnowski, 1995; Delorme & Makeig, 2004).

Statistical analysis

For the demographics, independent t-tests were performed. A chi-square test was performed for sex differences and the robust counterpart of the t-test as implemented in the *WRS2* (version 1.1-4) package (Mair & Wilcox, 2020) was used when assumptions were violated. All analyses were performed in *R* (version 4.2.0) using *Rstudio* (version 2022.07.1). For the EEG data, after inspection of the time course and the spatial distribution of the components of interest, the microvolt scaled amplitudes of the max and min peaks were analyzed for two time windows (i.e., TF1SF1: 90 – 130 ms, TF3SF1: 30 – 70 ms; with TF denoting temporal factor and SF spatial factor). Subsequently, 2 (without Tinnitus vs. Tinnitus) x 2 (Isochronous vs. Random) x 2 (Standard vs. Deviant) x 2 (Position 1 vs Position 2) mixed ANOVAs were performed, separately for TF1SF1 and TF3SF1 using the *rstatix* (version 0.7.0) package (Kassambara, 2021). When checking the assumptions, some outliers were identified and two extreme outliers excluded (i.e., exceeding the interquartile range by a threefold), as they were outliers for several combinations of factors. Two participants without tinnitus were correspondingly excluded. Levene's tests were not significant, and normality was assumed based on the central limit theorem. All effects are reported as significant at $p < .05$. Effect sizes are reported as generalized eta squared ($\eta 2G$). Non-normally distributed variables such as the Hearing loss (HL) and duration of tinnitus in months underwent square root transformation (see supplementary material for further correlation analyses).

Results

Demographics

There was no significant age (t (50) = -1.36, p = .18, CI [-14.25, 2.74]) or sex difference between the two groups (χ2 (1, N = 2) = 0, p = 1). To assess handedness, the robust t-test that is based on a two-sample trimmed mean test was performed (Yuen, 1974). The result likewise indicated no significant difference between the two groups (ty (15.45) = 0.76, p = .46, CI [-7.13, 3.39]). There was also no significant difference in terms of education t (50) = 1.68, p = .1 CI [-0.15, -1.67]). However, in line with previous studies, hearing loss differed between the two groups (t (50) = -3.26, p = .002, CI [-18.44, -4.4]), indicating increased hearing loss in the tinnitus group. The TQ scores indicated an average mild tinnitus burden (Grade II) in the tinnitus group (MTQ = 37.3, $SDTQ$ = 17.6).

tsPCA results and selection of ERP components

The temporal-spatial PCA revealed seven temporal factors, explaining 95% of the total variance and seven spatial factors that explained 88% of the total variance. An overview of all 23 components that explained at least .5% of the total and .5% of the unique variance can be found in **Table 2.** Two temporal factors that reflected P50- or N100-like responses were selected (**Figure 2**). As the factor combinations are microvolt scaled reconstructed ERP components, P50 and N100 components of interest are referred to as P50- and N100-like responses. The first factor (TF1SF1) displayed a negative peak at channel FFC1h and explained 15.97% of unique variance. The frontocentral distribution included 42 channels (i.e., AFp1, AFp2, AF3, AFz, AF4, AFF5h, AFF1h, AFF2h, AFF6h, F5, F3, F1, Fz, F2, F4, F6, FFT7h, FFC5h, FFC3h, FFC1h, FFC2h, FFC4h, FFC6h, FFC8h, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FCC5h, FCC3h, FCC1h, FCC2h, FCC4h, FCC6h, C3, C1, Cz, C2, C4), with an absolute factor loading threshold of 0.6 (Dien, 2010). This corresponds to the N100 ERP component, considering previous literature on the temporal-spatial characteristics of the N100 and visual inspection (**Figure 3**) (Davis, Mast, Yoshie, & Zerlin, 1966; Hillyard, Hink, Schwent, & Picton, 1973; Luck, 2014). Another component, TF3SF1, explained 2.07% of unique variance and its frontocentral distribution, with absolute factor loadings of 0.6, encompassed 34 electrode sites (i.e., AF3, AFz, AF4, AFF1h, AFF2h, F3, F1, Fz, F2, F4, F6, FFC5h, FFC3h, FFC1h, FFC2h, FFC4h, FFC6h, FC5, FC3, FC1, FCz, FC2, FC4, FCC5h, FCC3h, FCC1h, FCC2h, FCC4h, C3, C1, Cz, C2, CCP3h, CCP1h). Previous literature shows that the P50 has a frontocentral maximum and peaks around 40 – 80 ms (Patterson et al., 2008). Although the absolute voltage of the peak channel was negative, indicating heterogeneities across conditions, visual inspection, time course, and spatial distribution suggest that TF3SF1 corresponds to the P50 ERP component (**Figure 4**).

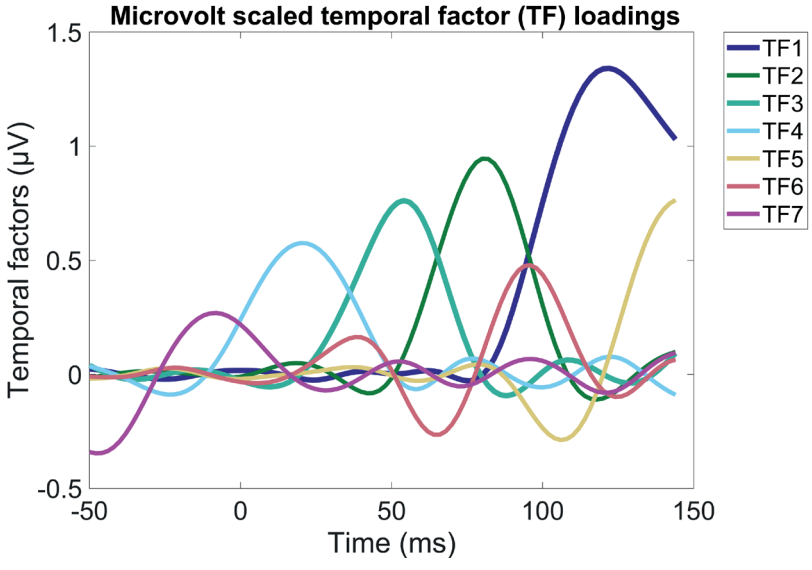

Figure 2. Overview of the temporal factors. Microvolt scaled temporal factors based on temporal-spatial principal component analysis of ERP data.

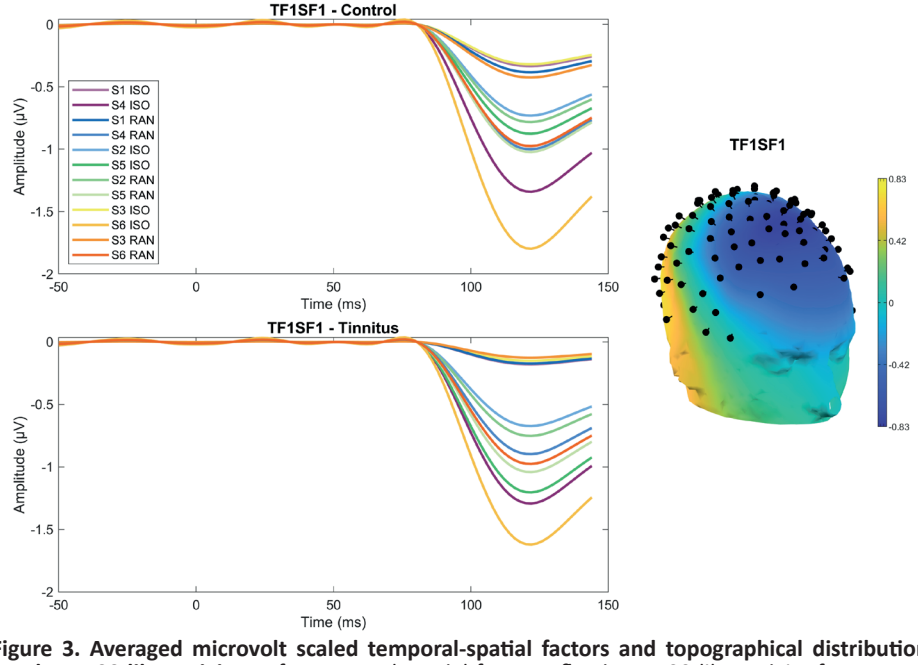

Figure 3. Averaged microvolt scaled temporal-spatial factors and topographical distribution for the N100-like activity. Left: Temporal-spatial factor reflecting N100-like activity for persons without tinnitus (Control, top) and persons with tinnitus (Tinnitus, bottom). Right: Topographical depiction of TF1SF1 for all conditions and stimuli, and both groups combined.

Table 2. Principal components explaining at least .5% of the total variance and .5% of the unique variance.

Principal component	Peak latency (ms)a	Peak channel (-)b	Peak channel (+)b	Peakc	Total variance explained	Unique variance explained
TF1SF1	122	FFC1h	O10	-	26.53%	15.97%
TF1SF2	122	CCP1h	Fp1	+	6.97%	4.11%
TF1SF3	122	Fp1	TP9	+	5.19%	3.09%
TF1SF4	122	FTT9h	FTT8h	+	2.39%	1.44%
TF1SF5	122	O10	CCP5h	+	1.09%	0.67%
TF1SF6	122	FC5	PO7	+	0.97%	0.60%
TF2SF1	80	FFC1h	O10	-	7.63%	3.78%
TF2SF2	80	CP2	Fp1	+	2.28%	1.09%
TF2SF3	80	Fp1	TP9	+	1.67%	0.86%
TF2SF4	80	P7	FTT8h	+	1.41%	0.71%
TF2SF5	80	PO9	CCP5h	+	1.17%	0.53%
TF2SF6	80	FFC5h	PPO9h	-	1.11%	0.52%
TF3SF1	54	FFC1h	PPO10h	-	4.62%	2.07%
TF3SF2	54	F9	Pz	-	1.57%	0.68%
TF3SF3	54	O9	Fp1	+	1.44%	0.63%
TF3SF4	54	P7	C6	-	1.22%	0.55%
TF4SF1	20	FFC1h	PO8	+	2.69%	1.51%
TF4SF2	20	F10	CPP1h	+	1.43%	0.80%
TF4SF3	20	TP7	C4	-	0.98%	0.55%
TF5SF1	144	TPP9h	FFC1h	+	3.32%	2.58%
TF5SF2	144	F10	Pz	+	0.84%	0.66%
TF6SF1	96	FFC3h	TPP9h	+	2.39%	1.29%
TF7SF1	-48	PPO5h	AFF2h	-	0.80%	0.64%

[a] Time point with the largest voltage.
[b] Channel with the greatest voltage for positive and negative voltages.
[c] Whether the negative or positive peak channel had a greater absolute voltage.

P50-like activity (TF3SF1)

There were significant main effects of *temporal structure* (i.e., smaller values for the isochronous condition), $F(1,48) = 20.54$, $p < .0001$, $\eta 2G = .064$, *formal structure* (i.e., larger values for deviants), $F(1,48) = 49.02$, $p < .0001$, $\eta 2G = .087$, and *position* (i.e., smaller values for position 2), $F(1,48) = 150.25$, $p < .0001$, $\eta 2G = .337$. Additionally, there were interaction effects of *temporal structure* and *formal structure*, $F(1,48) = 4.64$, $p = .036$, $\eta 2G = .005$, and of *temporal structure* and *position*, $F(1,48) = 38.52$, $p < .0001$, $\eta 2G = .085$. Post-hoc analyses consisted of Bonferroni corrected simple

pairwise comparisons and confirmed significant differences between the isochronous and random condition for deviant, t(49) = -4.07, $p < .001$, and standard, t(49) = -4.43, $p < .0001$, tones. Deviant and standard responses also differed within the isochronous t(49) = 4.88, $p < .001$ and the random t(49) = 6.42, $p < .001$ condition. (**Figure 5**). For the *temporal structure* x *position interaction*, post-hoc tests showed significant differences between the isochronous and random condition for position 2, t(49) = -6.01, $p < .001$, but not for position 1, t(49) = 0.821, $p = .416$ responses. In addition, significant differences between position 1 and position 2 were obtained for the isochronous, t(49) = 11.2, $p < .001$ and the random, t(49) = 7.2, $p < .001$ condition (**Figure 5**).

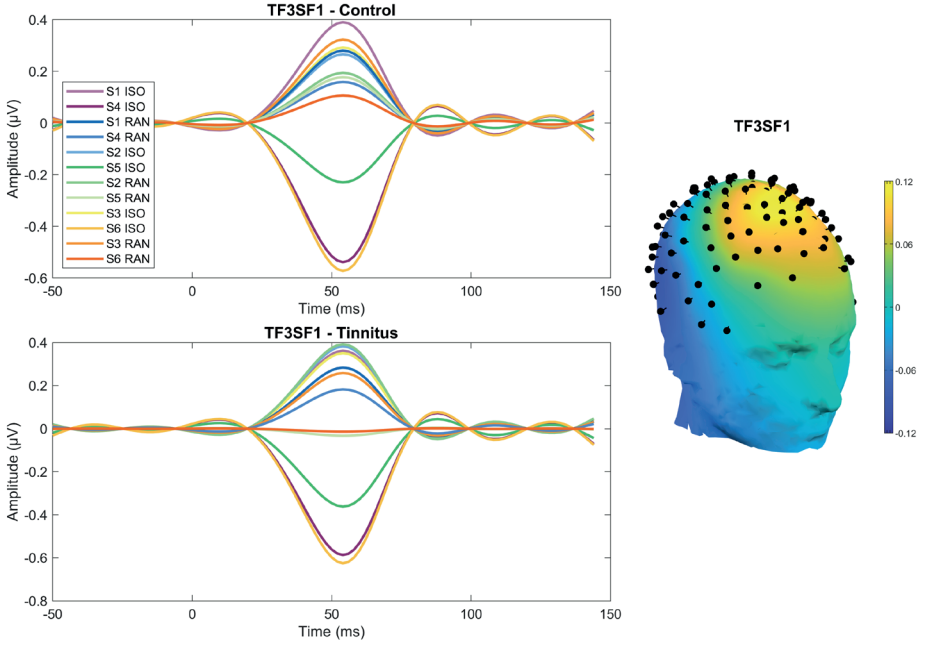

Figure 4. Averaged microvolt scaled temporal-spatial factors and topographical distribution for the P50-like activity. Left: Temporal-spatial factor reflecting P50-like activity for persons without tinnitus (Control, top) and with tinnitus (Tinnitus, bottom). Right: Topographical depiction of TF3SF1 for all conditions and stimuli, for both groups combined.

N100-like activity (TF1SF1)

As expected, there were significant main effects of *temporal structure* (i.e., isochronous versus random) indicating more negative values for the isochronous condition, $F(1,48) = 21.96$, $p < .0001$, $\eta 2G = .028$, *formal structure* (i.e., standards versus deviants), reflecting more negative values for deviants, $F(1,48) = 45.12$, $p < .0001$, $\eta 2G = .057$, and

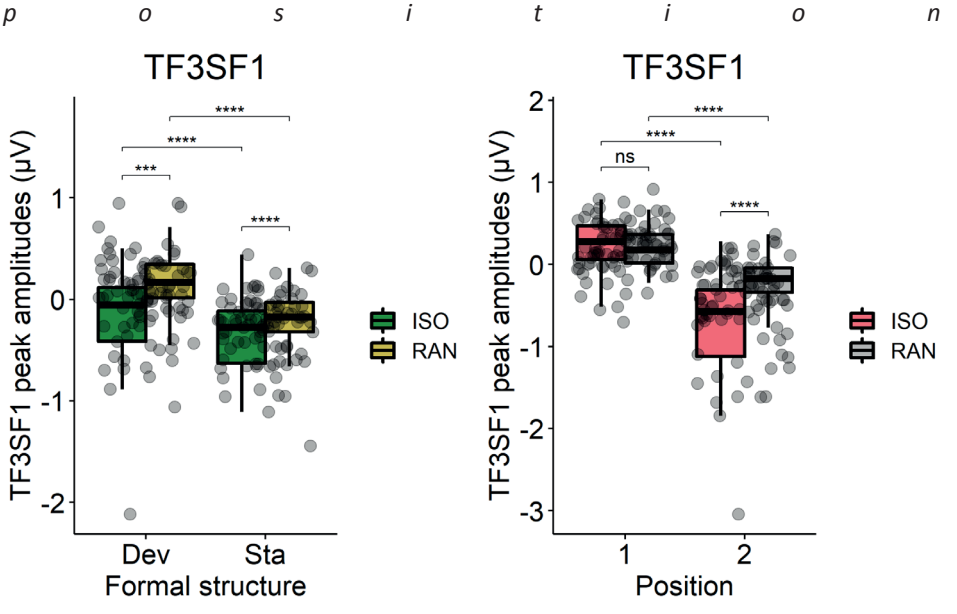

Figure 5. Depiction of the peak amplitudes for the P50-like activity. Peak amplitudes in microvolts for the third temporal and first spatial factor (TF3SF1) for the temporal structure x formal structure (left) and temporal structure x position (right) interaction. Abbreviations: Sta: standard, Dev: deviant, ISO: isochronous condition, RAN: random condition, *** p ≤ .001.

(i.e., position 1 versus position 2), indicating more negative values for position 2, $F(1,48) = 91.46$, $p < .0001$, $\eta 2G = .248$. Additionally, there were interactions of *temporal structure* and *formal structure*, $F(1,48) = 19.42$, $p < .0001$, $\eta 2G = .01$, *temporal structure* and *position*, $F(1,48) = 33.34$, $p < .0001$, $\eta 2G = .038$, and *formal structure* and *position*, $F(1,48) = 11.17$, $p = .002$, $\eta 2G = .008$. For the *temporal structure* x *position interaction*, post-hoc tests showed significant differences between the isochronous and random condition for position 2, $t(49) = -7.38$, $p < .001$, but not for position 1, $t(49) = 0.585$, $p = .561$ responses. In addition, significant differences between position 1 and position 2 were obtained for the isochronous, $t(49) = 9.96$, $p < .001$ and the random, $t(49) = 6.54$, $p < .001$ condition (**Figure 6**).

Finally, three-way interactions of *temporal structure* x *formal structure* x *position* was significant, $F(1,48) = 33.26$, $p < .0001$, $\eta 2G = .013$, and *group* x *temporal structure* x *formal structure interaction* were significant, $F(1,48) = 4.65$, $p = .036$, $\eta 2G = .002$. Post-hoc analyses consisted of a Bonferroni corrected simple-two way interaction at each level of *group*, resulting in significant main effects of *temporal structure*, $F(1,22) = 9.94$, $p = .03$, $\eta 2G = .049$, and *formal structure*, $F(1,22) = 19.2$, $p < .01$, $\eta 2G = .072$, in

persons without tinnitus, as well as in persons with tinnitus (i.e., *temporal structure*: $F(1,26) = 12.1$, $p = .012$, $\eta 2G = .031$, *formal structure*: $F(1,26) = 27.1$, $p < .001$, $\eta 2G = .087$). However, only persons without, $F(1,22) = 13.1$, $p = .012$, $\eta 2G = .033$, but not with tinnitus, $F(1,26) = 4.91$, $p = .216$, $\eta 2G = .003$, showed the *temporal structure* x *formal structure interaction*, that remained significant after Bonferroni correction. For persons without tinnitus, a simple simple main effect further indicated a significant difference between temporal conditions selectively for the deviant tones, $F(1,22) = 14.9$, $p < .001$, $\eta 2G = .132$, but not for standard tones, $F(1,22) = 0.41$, $p = .53$, $\eta 2G = .002$. Finally, following up on the effect of temporal structure for deviant tones in persons without tinnitus, Bonferroni corrected simple simple pairwise comparisons showed a significant difference between the isochronous and the random condition for deviant tones for persons without tinnitus, $t(22) = -3.86$, $p < .001$ (**Figure 7**).

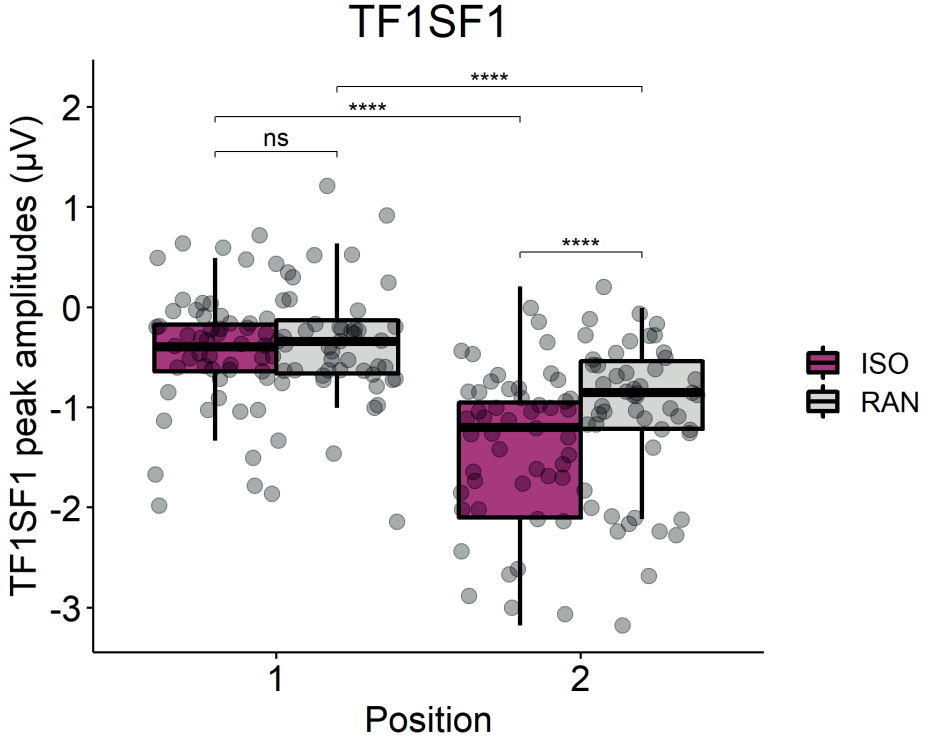

Figure 6. Depiction of the peak amplitudes for the N100-like activity. Peak amplitudes in microvolts for the first temporal and first spatial factor (TF1SF1) temporal structure x position interaction. Abbreviations: ISO: isochronous condition, RAN: random condition, *** $p \leq .001$.

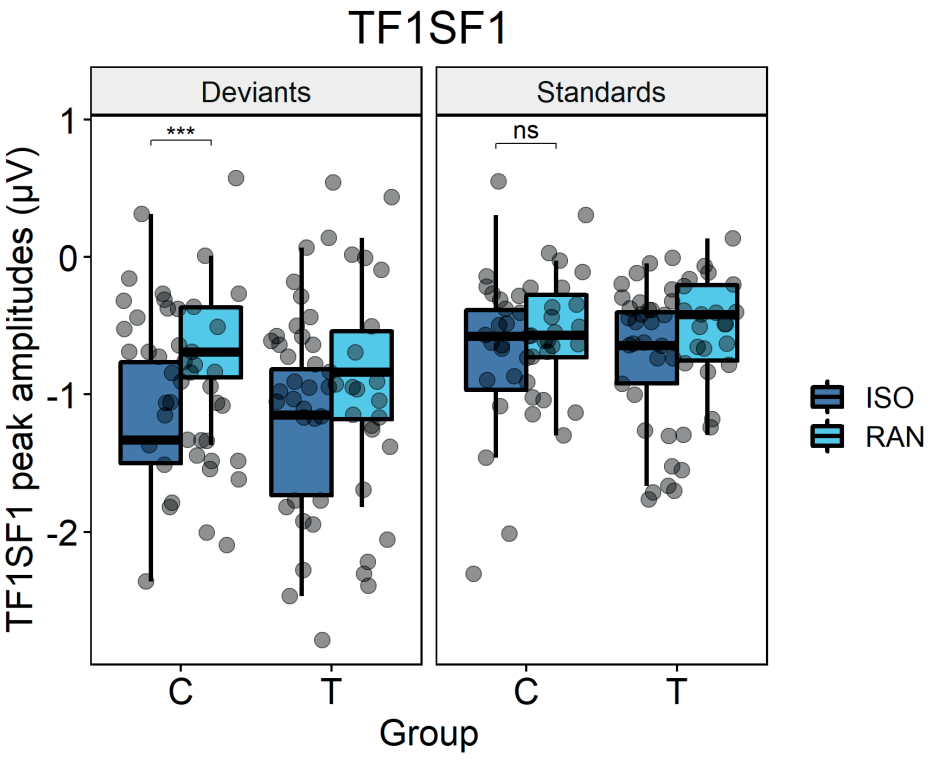

Figure 7. Depiction of the peak amplitudes for the group differences for the N100-like activity. Peak amplitude differences in microvolt for the first temporal and spatial factor (TF1SF1) for the simple pairwise comparisons. Abbreviations: ISO: isochronous condition, RAN: random condition, C: control Group/persons without tinnitus, T: persons with tinnitus, *** $p \leq .001$.

Discussion

This study investigated modulations of the P50- and N100-like activity in response to three different dimensions of stimulus predictability in persons with and without tinnitus. Manipulations of predictability altered the formal and temporal structure as well as the position of tones presented in pairs. This binary grouping made the setup comparable to classical binary SG paradigms. P50-like activity indicated expected effects of formal structure, temporal structure, and position in both groups. In other words, P50 amplitudes were smaller for standard than deviant tones, smaller for isochronous than random stimulus timing, and smaller in response to the second than the first tone of tone pairs, confirming a classical SG effect in both groups. These results confirm the effectiveness of a paradigm to simultaneously assess formal-, temporal- and position predictability. Additionally, there was a significant difference between the temporal conditions for the second tone in pairs, while this was not the case for the first tone.

This again indicates a stronger amplitude reduction in the isochronous than the random condition in both groups. This overall pattern repeated in the N100-like activity, while globally, amplitudes for the isochronous sequence were more negative than for the random sequence. However, amplitudes in N100-like activity were larger for deviant than for standard tones in the isochronous timing condition in persons without tinnitus only. Previous research reported that participants respond faster when stimuli are presented in a temporally regular than irregular context (Lange, 2009; Rohenkohl, Cravo, Wyart, & Nobre, 2012) and that temporal predictability facilitates stimulus detection (Lawrance, Harper, Cooke, & Schnupp, 2014). At the neurophysiological level, the suppression of early ERP responses to expected stimuli is a well-established phenomenon (Bendixen et al., 2012; Costa-Faidella et al., 2011; Lange, 2009; Schwartze et al., 2013). Therefore, the current findings for temporal predictability are in line with these previous findings.

However, the current study did not reveal differences for position predictions (SG) between persons with and without tinnitus in P50- and N100-like activity. Previously, Campbell et al. (2018) found a correlation for tinnitus severity, suggesting decreased gating in the Pa component when tinnitus burden increased. However, similar to the current results, they reported no group differences in SG for the Pa, P50, N100 or P200 components (Campbell et al., 2018). Similar P50 results were reported by Dornhoffer et al. (2006). Compared to the current study, participants in the Campbell et al. (2018) study had similar hearing thresholds but were younger (i.e., on average between 20 and 22 years) and their tinnitus handicap was very low (i.e., 0 – 14). A tinnitus handicap inventory (THI) score can range between 0 - 100 and scores between 0 - 16 indicate no or only a slight handicap (Lee, Ra, & Kim, 2014; Newman et al., 1996). Here, we administered the TQ and not the THI, even though both instruments have shown high convergent validity (Baguley, Humphriss, & Hodgson, 2000). In addition, the paradigms differed in terms of the intra-PI (500 ms) and the inter-PI (7 s) (Campbell et al., 2018). As the current paradigm used shorter intra-PIs and inter-PIs and to avoid double dipping, we applied tsPCA, a data-driven analysis that can delineate overlapping processes and can therefore enhance the signal-to-noise ratio (Dien, 2012; Foti et al., 2009). Moreover, in the current study, N100-like activity was frontally located, which might be explained by age of in the current participant sample (Paitel & Nielson, 2021). In Dornhoffer et al. (2006), the age range was similar to the current study. However, another tinnitus severity questionnaire (i.e., tinnitus severity index questionnaire) was administered. With different intra-PIs (i.e., 250 ms, 500 ms, 1000 ms), there were no group differences for P50 SG (Dornhoffer et al., 2006). Overall, the current study thus produced similar results as Campbell et al. (2018) and Dornhoffer et al. (2006), despite methodological

differences between the studies. This confirms the robustness of the results, suggesting that SG dysfunctions in tinnitus are likely more subtle than assumed.

Most importantly, we observed SG effects in persons with and without tinnitus, indicating successful processing of position predictions and an associated reduced response. Early SG research focused on persons with schizophrenia, showing that SG is dysfunctional in this group (Adler et al., 1982; Patterson et al., 2008). Other research observed a similar pattern in persons with Alzheimer's disease (Jessen et al., 2001) or ADHD (Davies, Chang, & Gavin, 2009; Holstein et al., 2013). Similar to the current and Campbell et al. (2018) findings, unaltered SG in persons with tinnitus was also reported in high-functioning children along the autism spectrum (Kemner, Oranje, Verbaten, & Engeland, 2002; Orekhova et al., 2008), and in patients with obsessive-compulsive disorder (de Leeuw, Oranje, van Megen, Kemner, & Westenberg, 2010). In the current study, we now show that for the P50-like and the N100-like activity, predictions regarding formal structure and position are intact in both groups in a temporally predictable context, indicating intact binary auditory stimuli filter mechanisms in persons with tinnitus.

For the N100-like activity, however, a different pattern emerged for deviance processing in the two timing conditions in persons with and without tinnitus. This observation can be linked to different attentional processing for deviant events in persons with and without tinnitus. Altered attention in persons with tinnitus has previously been proposed by Roberts et al. (2013). Roberts et al. (2013) proposed a qualitative model, in which attention allocation changes following a mismatch between the incoming auditory input and the sound representation generated in the auditory cortex. In addition, a meta-analysis investigated behavioral and electrophysiological measures of attention in persons with tinnitus and confirmed that later attentional processes are altered in persons with tinnitus as indicated by reduced mismatch negativity (MMN) and P300 amplitudes, although the heterogeneity of the tinnitus populations and methods limit precise interpretations of the underlying mechanisms (Vasudevan, Ganapathy, Palaniswamy, Searchfield, & Rajashekhar, 2021). When assessing the N100 component in persons with tinnitus, reduced N100 amplitudes were observed for persons with distressing (i.e., decompensated) tinnitus (Jacobson & McCaslin, 2003). Moreover, persons with low and high tinnitus-related distress showed differences in N100 activity (Delb et al., 2008). More specifically, in an unattended condition, in which participants had to ignore tones and think of something pleasant, differences were found between persons with low tinnitus distress and high tinnitus distress (more negative N100 for high distress) and between persons without tinnitus and high tinnitus distress (more negative N100 for high distress). In the attended condition, N100 amplitudes

of persons with high distress were more negative than without tinnitus (Delb et al., 2008). Other research on auditory attention in tinnitus (Roberts et al., 2013), suggests facilitatory cholinergic neuromodulation in cortico-subcortical pathways at the level of the ventromedial prefrontal cortex and basal forebrain, which could reinforce aberrant neural synchrony in persons with tinnitus. Interestingly, it was reported that activity in fronto-parietal regions differs in persons with tinnitus when they are presented with tinnitus-specific frequency sounds as opposed to a control frequency (Salvari et al., 2023). These findings may indicate why a more efficient adaptation to deviant tones was observed in persons without tinnitus than in persons with tinnitus and suggests altered auditory attention allocation in response to deviant tones in the tinnitus group. Along these lines, the current findings may indicate a shifting of attentional bias toward the tinnitus percept or altered redirection of selective auditory attention away from it. Future research should therefore delineate how auditory predictions are influenced by tinnitus-specific frequencies (i.e., regularly 2-4 kHz in tinnitus linked to noise induced hearing loss (Eggermont & Roberts, 2004)) for the P50- and N100-like components, respectively.

Lastly, when working with a clinical population such as persons with tinnitus, controlling for hearing loss, age, and/or hyperacusis at the same time is challenging. Tinnitus is more prevalent in older persons and often accompanied by some degree of hearing loss (Axelsson & Ringdahl, 1989; Knipper, Van Dijk, Nunes, Rüttiger, & Zimmermann, 2013; Nelson & Chen, 2004), although it can also occur without altered hearing thresholds (Roberts et al., 2010; Weisz et al., 2006). The average hearing loss in the current tinnitus sample was very mild and associated with no impairment at all or with slight difficulties (Olusanya, Davis, & Hoffman, 2019). Research that includes persons with tinnitus with and without hearing loss and comparisons to hearing-matched persons without tinnitus remains scarce. One EEG study that investigated prediction errors for auditory false perceptions and phantom perceptions in persons with tinnitus assigned participants to groups with mild or severe hearing loss and compared them to a group of persons with schizophrenia (Ahn et al., 2022). The results showed that auditory ERP responses for self-generated sounds were not suppressed in persons with tinnitus + severe hearing loss (n = 15) and persons with schizophrenia (n = 10), whereas the typical suppression was observed in persons without tinnitus (n = 23) and in persons with tinnitus + mild hearing loss (n = 8) (Ahn et al., 2022). However, the degree of hearing loss in the tinnitus + hearing loss group exceeded the level of hearing loss in the current group, while also no full high-frequency audiometry was performed here. Similarly, an MRI study that compared persons with hearing loss, tinnitus + hearing loss, and controls showed that

tonotopic maps for the hearing loss + tinnitus were more similar to controls relative to persons with hearing loss only (Koops et al., 2020). Therefore, it was concluded that tinnitus might be a side product of dampened cortical reorganization and not the result of it (Koops et al., 2020). However, considering the overall mild hearing loss, it is likely that hearing loss only had a minor influence on current results.

The results show that the adopted paradigm permits assessing three dimensions of auditory prediction (i.e., formal-, temporal-, and position). Classic position-based SG was not altered in persons with and without tinnitus for the P50-like activity. However, for the N100-like activity, deviance processing was further modulated by temporal regularity only in persons without tinnitus but not in persons with tinnitus. Hence, it seems likely that temporally regular and thus fully predictable stimulation facilitates deviance processing in persons without tinnitus and that this mechanism is altered in persons with tinnitus. Auditory filtering as indexed by classical SG effects for binary auditory stimuli seems thus not substantially different in persons with and without tinnitus. It rather seems that tinnitus alters attention-allocation in response to the deviant, i.e., unpredicted or at least less predictable auditory events. This finding might indicate a shifting attentional bias towards the tinnitus sound that may be accompanied by dysfunctional allocation of selective auditory attention to other sounds.

Supplementary Material

Relationship between classical sensory gating, HL, TQ and duration of tinnitus

Methods

Pearson correlations were performed on the standard – standard tone pair in the isochronous condition as implemented in the *rstatix* package. SG was quantified in terms of peak amplitude differences (Position 1 – Position 2). In general, SG can be quantified by calculating the SG ratio, or the SG difference, while the latter is recommended (Rentzsch, Jockers-Scherübl, Boutros, & Gallinat, 2008; Smith et al., 1994).

Results

TF1SF1

When correlating the SG difference scores with the amount of average HL per subgroup, a non-significant positive relation between the SG values and the amount of hearing loss was observed. In the control group improved SG correlated non-significantly with increased HL (r (21) = .35, p = .1, CI [-.07, 0.66]), similarly to the tinnitus group(r (25) = .21, p = .3, CI [-.19, .55]). For the tinnitus burden, assessed by the TQ in the tinnitus group, SG values exhibited a non-significant negative relation between SG difference scores and TQ, (r (25) = -.2, p = .33, CI [-.54, .2]). When focusing on the duration of tinnitus (in months) and SG, a non-significant positive correlation was found for the tinnitus group, r (25) = .16, p = .42, CI [-.23, .51]).

TF3SF1

For the TF3SF1 component, a similar pattern was observed regarding the directions and the level of significance of the correlations. In the control group improved SG correlated non-significantly with increased HL (r (21) = .36, p = .095, CI [-.07, 0.67]), similarly to the tinnitus group(r (25) = .03, p = .88, CI [-.35, .41]). For the tinnitus burden, assessed by the TQ in the tinnitus group, SG values exhibited a non-significant negative relation between SG difference scores and TQ, (r (25) = -.17, p = .41, CI [-.51, .23]). When focusing on the duration of tinnitus (in months) and SG, a non-significant negative correlation was found for the tinnitus group, r (25) = -.016, p = .94, CI [-.39, .37]).

5

Chapter 5

General discussion

General discussion

The purpose of this dissertation was to advance the current knowledge about the characteristics and the role of predictions in audition and in altered listening experiences, focusing on older adults and persons with tinnitus. To this end, a literature review and two empirical studies were conducted that assessed how formal and temporal predictions evolve in older adults and in persons with tinnitus. Literature on the functions of the auditory thalamus in tinnitus (**chapter 2**) was reviewed and electroencephalography (EEG) employed to assess the processing of differential predictions in audition (**chapter 3** and **4**). In the following, it will first be discussed how formal and temporal predictions shape auditory processing. Then, the current findings will be embedded in the context of the thalamocortical dysrhythmia hypothesis and finally, it will be elaborated on the concept of sensory gating and hallucinatory experiences.

'What' and 'when' predictions facilitate auditory processing

Adapting to the type and temporal occurrence of an event is essential for goal-directed behavior. Extracting information about 'what' (i.e., the form) and 'when' (i.e., the point in time) an auditory event might occur, impacts the coordination of different sensory modalities such as audition and vision (Bendixen et al., 2012; Einhäuser, da Silva, & Bendixen, 2020) and shapes the processing of language (Thiessen & Saffran, 2003) and music (Palmer, 2005). The previous chapters have shown that exploring formal and temporal predictions in audition is complex. This is partly due to divergent interpretations of what formal and temporal predictions entail. Another challenge is to relate the findings to conditions in which listening is altered.

How formal and temporal predictions are defined clearly shapes experimental paradigms and the interpretation of the respective findings. For example, temporal predictions might evolve along different time scales, spanning orders of magnitude from microseconds to circadian rhythms (Mauk & Buonomano, 2004). In audition, the most rapid temporal predictions involve sound localization based on the interaural time or level differences of sounds reaching the ears (Rayleigh, 1876). In bats, temporal differences of sounds reaching the ears as small as 0.01 microseconds can be detected (Simmons, Ferragamo, Moss, Stevenson, & Altes, 1990). Other temporal predictions might distinguish beat-based from interval-based timing, or temporally regular from random sound sequences (Nobre & Van Ede, 2018). Formal predictions on the other hand, were described as feature expectations (Nobre & Van Ede, 2018; Schwartze & Kotz, 2013) or spatial processing (Mauk & Buonomano, 2004) and encompass predictions

about the quality of upcoming tones or patterns such as melodies. Thus, differentiating 'what' and 'when' predictions allows breaking down prediction in audition into its basic constituents as an approximation of how humans process sounds in naturalistic environments. Consequently, the common denominator of the findings presented in this dissertation, (i.e., 'what' and 'when' predictions) will be discussed, followed by reflections on how aging and tinnitus might affect these predictions. For parts of the current empirical work, 'when' predictions were multilayered, consisting of temporal and position predictions.

The two empirical studies of this dissertation investigated formal-, temporal- and position predictions in healthy younger and older adults (**chapter 3**) and in persons with and without tinnitus (**chapter 4**), focusing on EEG auditory ERP components like the P50 and N100. The results reported in **chapter 3** and **4** confirmed that formal and temporal predictions interact and can facilitate auditory processing in younger but less so in older adults, whereas no corresponding group differences were observed for persons with and without tinnitus in the P50 response. For the N100, the temporal context facilitated deviance processing in the control group, but not in the tinnitus group, whereas no group differences were observed between older and younger participants. This result is in line with previous studies, reporting that 'what' and 'when' predictions interact and that temporal predictability enhances repetition suppression (Costa-Faidella et al., 2011). In addition, Auksztulewicz et al. (2018) found that 'what' and 'when' predictions interacted as evident in activity of the superior temporal gyrus, while modeling indicated that they rely on complimentary processes in auditory and motor brain areas. More specifically, 'what' predictions were found to increase short-term plasticity in auditory areas, whereas 'when' predictions were associated with increased synaptic gain in motor areas (Auksztulewicz et al., 2018). Schwartze, Rothermich, et al. (2011) also investigated the interaction of formal and temporal predictions in young healthy adults, while also manipulating attention. Results indicated that the P50 did not display a significant interaction between formal and temporal predictions and that the attention manipulation did not affect the results (Schwartze et al., 2013). In the N100, formal and temporal predictions interacted as a function of attention (Schwartze et al., 2013). The current findings partially align with the findings reported by Schwartze et al. (2013), such that temporal and formal predictions interacted at the level of the N100 but also the P50. Altered sound processing in these populations combined with methodological differences in the paradigm might explain these differences and are discussed further below.

Neural inhibitory processing can be defined as the suppression of activity of one neuron by another neuron and is altered in aging (Caspary, Ling, Turner, & Hughes, 2008; Herrmann & Butler, 2021). Therefore, in aging, overall reduced inhibitory processing might lead to changes in the mechanisms underlying formal and temporal predictions. In general, aging has been linked to reduced cognitive control (including working memory, attention, and inhibition), due to reduced dopamine signaling to prefrontal cortices (Braver & Barch, 2002). The current findings show that temporal regularity did not facilitate deviance processing in older adults as it did in younger adults (**chapter 3**). This age effect is comparable to one reported in a previous study that assessed temporal regularity in younger and older adults (Herrmann, Buckland, & Johnsrude, 2019). Herrmann et al. (2019) found increased responsiveness in the auditory cortex in older adults, whereas processing of temporally regular sound sequences assessed by sustained neural activity was reduced. This occurred when activity was compared to neural synchronization, while in younger adults, the result was reversed (Herrmann et al., 2019). Moreover, neural synchronization to 4-Hz amplitude modulation was enhanced in older compared to younger adults (Herrmann et al., 2019). From these findings, the authors inferred that in older adults, temporal sound regularity is over-represented in the auditory cortex and under-represented in the auditory network involving also brain regions such as the hippocampus, parietal cortex and frontal cortex (Herrmann et al., 2019). The authors thus concluded that in older adults, sensitivity to temporal regularity of sounds is altered in the auditory cortex and higher-level cortices (Herrmann et al., 2019). Another explanation might be that middle-aged or older adults use different attentional control mechanisms, when confronted with 'when' predictions than younger adults (Herrmann et al., 2023). For this experiment, attentional control mechanisms included the 'hazard-rate', where faster responses to stimuli are expected when a time window was indicated by a cue, reflecting successful allocation of attention in time (Herrmann et al., 2023; Nobre et al., 2007). Herrmann et al. (2023) found that younger and older adults might engage different brain regions (for younger adults superior parietal and middle-aged and older adults posterior temporal areas) when recruiting attention for temporal predictions (Herrmann et al., 2023). It is therefore possible that the altered processing of 'what' and 'when' predictions in healthy older adults reflects impaired inhibitory processing, which might be linked to different processing of temporal sound regularity or altered attentional control mechanisms. Lastly, for the results presented in **chapter 4**, the age range was quite broad, meaning that the sample consisted of younger and older adults (tinnitus = 27 y – 69 y, controls = 23 y – 68 y). This makes it difficult to conclude how age affects prediction in sound

sequences. Consequently, the heterogeneous age range in **chapter 4** could have diluted the results, thereby decreasing statistical power.

Another factor inevitably linked to aging and sound processing is hearing loss (Herrmann & Butler, 2021). Animal models (Schmiedt, Mills, & Boettcher, 1996; Sergeyenko, Lall, Liberman, & Kujawa, 2013) and human studies (Makary, Shin, Kujawa, Liberman, & Merchant, 2011) suggested that cochlear neural degeneration occurs in healthy aging and that subsequent hearing loss can be difficult to detect as it can also be 'hidden' (Weisz et al., 2006). 'Hidden hearing loss' means that affected persons have a normal audiogram, although their cochlea is damaged (Plack, Barker, & Prendergast, 2014; Schaette & McAlpine, 2011). Subsequently, it has been proposed that aging and hearing loss might underlie decreased inhibition associated with lower levels of GABA in the auditory cortex (Gao et al., 2015; Herrmann & Butler, 2021). Going back to the current findings, hearing loss was an exclusion criterion in the study presented in **chapter 3**, which might explain its minimal impact on the EEG results. However, since extended high-frequency audiometry or assessment of cochlear function via otoacoustic emissions or click-evoked electrocochleography were not performed (see for example: (Liberman, Epstein, Cleveland, Wang, & Maison, 2016)) to reveal hidden hearing loss, participants could have suffered from less detectable hearing loss. In **chapter 4**, hearing loss was assessed via pure tone audiometry and significantly differed between groups, although it was still mild on average. Therefore, the results presented in **chapter 4** do not fully allow attributing the findings to tinnitus, as the levels of hearing loss were not matched. However, as the hearing loss levels were mild on average, it was assumed that hearing loss did not alter the results substantially, even considering hidden hearing loss. In the future, extensive audiological assessments, preferably behavioral audiometry combined with cochlear function assessments should be performed to match participants for high-frequency and 'regular'-frequency hearing loss.

Adding further complexity to the elaboration of the current findings on formal and temporal auditory predictions, hearing loss and older age are considered risk factors for developing tinnitus and/or hyperacusis (Knipper et al., 2013). Tinnitus is a heterogeneous disorder and with increasing severity, tinnitus-related comorbidities, such as insomnia, anxiety or hearing distress increase as well (Beukes, Manchaiah, Allen, Andersson, & Baguley, 2021). In the current findings, tinnitus severity was mild on average (Grade II; Tinnitus Questionnaire), while participants were matched for sex, age, and education (**chapter 4**). The mild tinnitus severity was similar to tinnitus severity's levels in Campbell et al. (2018) and Dornhoffer et al. (2006). These authors also observed no

group differences for the majority of the assessed ERP components. However, it is possible, that participants with severe tinnitus process formal and temporal predictions differently from persons with mild tinnitus. Interestingly, Walpurger et al. (2003) tested two groups of persons with tinnitus (i.e., severe and less severe tinnitus complaints) and a third group without tinnitus. The participants performed a habituation task and were presented with sequences in which tones were either 1, 2, or 3 seconds apart (Walpurger et al., 2003). They reported that habituation of the N100-P200 vertex amplitude difference was preserved in persons with less severe tinnitus but reduced in persons with severe tinnitus (Walpurger et al., 2003). However, Walpurger et al. (2003) did not manipulate temporal predictability, differentiating between isochronous and random sequences, but studied habituation in isochronous sequences.

More detailed findings presented in **chapter 3** and **4** of this dissertation can illustrate how the discussed conditions (i.e., aging, hearing loss, and tinnitus) might co-depend on and need to be considered when interpreting the current findings. Results presented in **chapters 3** and **4** suggest that for the P50 component, the interaction between 'what' and 'when' predictions in younger adults (**chapter 3**) was like the P50 results in **chapter 4**, however, combined for persons with and without tinnitus. As previously discussed, this could stem from the diluted age range in the study presented in **chapter 4**. Moreover, the differences in hearing loss or tinnitus severity levels might have affected the results as well. It is therefore necessary to be cautious when comparing the P50 results of both chapters. Another possibility is that the modifications to the paradigm presented in **chapter 3** and **4** might have influenced the results. This possibility will be discussed below. Future studies should therefore aim at controlling for age, hearing loss, as well as tinnitus severity. Ideally, investigating subgroups of different tinnitus severity might inform about how formal and temporal predictions might evolve with increasing tinnitus severity.

It is generally challenging to match participant groups simultaneously on multiple characteristics, thereby rendering recruitment as time consuming. In the current studies, matching the participants for specific criteria was linked to multiple constraints, but predominantly to recruiting participants during the ongoing COVID-19 pandemic. Patients and older adults were far more hesitant to participate due to the length of the EEG measurements and the confined recording space.

Other methodological considerations for the future entail adaptations of the stimulus intervals. The paradigm presented in **chapter 3** was adapted for the empirical investigation reported in **chapter 4** by adding paired stimuli and shortening the time

intervals between tones. The goal of the study presented in **chapter 4** was to assess formal-, temporal- and position-predictions in parallel, which was successful. However, previous research implementing paired stimuli used longer pair timings (i.e., timing between tones in a pair). In a classical sensory gating experiment, Adler et al. (1982) implemented 500 ms pair timing, while in **chapter 4** for the isochronous sequence, the interval was 200 ms. In the random sequence, the pair timing varied between 100 - 300 ms. How these adaptations of the design might have influenced the electrophysiological responses and should be further assessed. For example, a longer interval could lead to less overlap of auditory ERP components, which would lead to improved baseline results, thus reducing potential data drifts. In addition, the timing intervals were not completely randomized, so that participants could still perceive the grouping of two tones, and the different intervals were balanced using a Williams Design (Williams, 1949). Therefore, how EEG responses based on 'true' randomness might diverge from the current random paradigm, could inform future investigations. For example, adapting the intervals between tones in a pair (i.e., pair timing) so that no grouping would be perceived, might result in stronger effects and less pronounced SG, as the 'true' randomness reduces prediction mechanisms. However, even alternatively introducing jitters to the random sequence presented in **chapter 4** might influence results, as jitter onsets are again not 'truly' randomized.

To disentangle possible superimposed ERP components due to the short time intervals between the tones, tsPCA was applied. TsPCA is a data driven analysis approach, aiming to improve more traditional methods to analyze ERPs, by objectifying the selection of time windows, ROIs, and by accounting for the fact that activity recorded at the scalp consists of a mixture of signals generated in the brain (Dien, 2012; Scharf, Widmann, Bonmassar, & Wetzel, 2022). Although tsPCA is a widely used method, some choices could have influenced the results and should be elaborated. First, the method to extract the number of factors could have led to extracting too few factors (i.e., underextraction). As presented in **chapter 4**, a restricted solution via the Parallel Test (Horn, 1965) was used. Scharf et al. (2022), for example, advocated to use the Empirical Kaiser Criterion (Braeken & van Assen, 2017), which was not applied, as it was not recommended by Dien (2012), and because its performance when factor cross-loadings are present is not well researched (Goretzko, Pham, & Bühner, 2021). Second, other researchers performed separate temporal PCAs for their experimental groups (i.e., younger vs. older adults) (Barry, De Blasio, & Cave, 2016), which is, however, not recommended by (Dien, 2010a) and was therefore not performed on the data presented in **chapter 4**. Dien (2012) and Scharf et al. (2022) argued that separate PCAs should only be performed if there are major differences between

the component structures, such as auditory vs. visual ERPs. Scharf et al. (2022) further suggested that separate PCAs should be conducted when substantial latency differences are expected, which was not the case for the data presented in **chapter 4**. It is however possible that systematic latency shifts occur between experimental conditions (see: (Barry, De Blasio, Fogarty, & Karamacoska, 2016)), which should be further explored in the future, by performing separate PCA analyses for conditions, where systematic latency shifts are expected. Last, the N100-like activity reported and discussed in **chapter 4** had a more frontal distribution and a longer latency relative to other N100 components (Luck, 2014; Pratt, 2011). However, these differences may also stem from the increased age of the participants in combination with hearing loss, as it was found that older adults with and without hearing loss had prolonged N100 latencies when presented with time-varying speech cues (Tremblay, Piskosz, & Souza, 2003).

Thalamocortical dysrhythmia and predictive networks in tinnitus

The thalamocortical dysrhythmia hypothesis states that in tinnitus, bottom-up deafferentation and impaired top-down noise-canceling lead to increases in theta oscillations that are coupled to gamma activity (De Ridder et al., 2015; Rauschecker et al., 2010). In tinnitus, there is a discrepancy between the predicted and actual auditory input, resulting from decreased sensory updating. This means that (often) deafferentation leads to hearing alterations in higher frequencies, and the central nervous system increases its gain mechanisms to maintain homeostasis (Sedley et al., 2016). Therefore, it is suggested that thalamocortical dysrhythmia is an adaptive mechanism to retrieve the auditory input that was altered by deafferentation in persons with tinnitus (De Ridder et al., 2015).

The role of the subcortical MGB is not widely considered in relation to tinnitus although it is, as described in **chapter 2**, involved in multiple aspects of sound processing (i.e., as an auditory and multisensory relay). In addition, the MGB has functional connections not only to primary cortical auditory areas but also to non-primary areas, such as the inferior frontal gyrus and cingulate cortices. In the review, it was argued that altered MGB functioning in tinnitus affects temporal processing. However, assessing temporal predictions with EEG in persons with and without tinnitus did not reveal group differences in temporal processing (**chapter 4**). As already discussed, these results might stem from the differences in hearing loss, the broad age range, the low severity of the tinnitus in the sample, or from methodological changes.

As discussed, the data analyses presented in **chapter 4** do not allow assessing the suggested neural architecture for temporal predictions in its entirety, as the focus was to assess different levels of sensory gating in tinnitus and the sensory gating literature is predominantly based on ERP research. Therefore, it is not possible to draw specific conclusions about how tinnitus might have altered the functioning of the whole brain network introduced in **chapter 2** from the current findings.

There is research investigating temporal predictions in the MGB in animal models of tinnitus (i.e., tinnitus was induced by noise-exposure), and findings indicated that noise-exposure led to impaired processing of temporal regularity (Zare et al., 2023). Moreover, restoring the processing of temporal regularity via high frequency deep brain stimulation (DBS) in the noise-exposed animals was not successful (Zare et al., 2023). Another finding suggests that high frequency DBS of the MGB in noise-exposed rats suppressed beta and gamma thalamocortical synchronization (van Zwieten et al., 2021). In humans, increased gamma and delta/theta activity was found in chronic tinnitus sufferers, who experienced episodes of enhanced tinnitus when assessed with MEG (Sedley et al., 2012). Finally, intracranial recordings of one patient indicated increased delta oscillations associated with tinnitus, which were present in auditory cortical areas as well as temporal, parietal and limbic regions (Sedley et al., 2015). This research suggests that DBS might be an alternative to treat tinnitus and it supports parts of the proposed network hypothesis in **chapter 2** by confirming altered thalamocortical dysrhythmia in tinnitus, coupled with impaired temporal regularity processing. Based on the current findings and the discussed literature, future investigations should collect data directly from the MGB together with information about functional connectivity and thalamocortical synchronization (i.e., cross-frequency coupling) between areas in the basal ganglia or primary and non-primary auditory areas in persons with tinnitus and without. This approach is currently being considered and initial evidence suggests that tinnitus burden decreased significantly after 1 year of DBS treatment (Devos et al., 2023).

Filtering (ir)relevant information – takes on sensory gating

The concept of sensory gating originated in schizophrenia research. In patients with schizophrenia, sensory gating impairments were described as deficits in attention and perception (McGhie & Chapman, 1961), such as a heightening of sensory vividness or increased awareness of background noises (Hetrick, Erickson, & Smith, 2012). Sensory gating was predominantly described as a P50 amplitude suppression effect for position

predictions (Adler et al., 1982). Next to additional electrophysiological correlates (i.e., other ERPs such as N100, P200, or beta & gamma oscillations) (Nguyen, Hetrick, O'Donnell, & Brenner, 2020; Rentzsch et al., 2008), behavioral measures of sensory gating were developed (Hetrick et al., 2012). To behaviorally assess sensory gating, a self-report questionnaire, the sensory gating inventory (SGI) was developed, identifying four perceptual dimensions: Perception Modulation (PM), Over-Inclusion (OI), Distractibility (D) and Fatigue-stress vulnerability (FS) (Hetrick et al., 2012). This measure has been widely used and translated into multiple languages, such as French (Micoulaud-Franchi, Hetrick, Boyer, et al., 2014), Persian (Mohebbi, Mahmoudian, et al., 2019), Japanese (Nobuyoshi et al., 2018), and Dutch (Brinkmann et al., 2023). Moreover, the questionnaire has been successfully used in various populations, such as ADHD (Micoulaud-Franchi et al., 2015; Sable et al., 2012) and schizophrenia (Micoulaud-Franchi, Hetrick, Aramaki, et al., 2014), and is considered of added value for patients with tics (Cohen, Leckman, & Bloch, 2013) or with Tourette syndrome (Isaacs & Riordan, 2020). In line with those examples, tinnitus and hearing loss have been linked to altered sensory gating, including changes in attention and auditory perception (Eggermont & Roberts, 2004; Walpurger et al., 2003). It seems that so far only one study investigated behavioral sensory gating with the SGI in persons with tinnitus (Mohebbi, Farhadi, Daneshi, & Mahmoudian, 2019). In this study, participants were classified as either experiencing compensated or decompensated tinnitus based on tinnitus loudness, awareness, and the severity of the tinnitus annoyance (Mohebbi, Farhadi, et al., 2019). Persons experiencing compensated tinnitus habituated to their tinnitus and are largely unaffected by it, while this was not the case in persons experiencing decompensated tinnitus. When groups were compared, results indicated impaired behavioral sensory gating in persons with decompensated tinnitus but not in persons with compensated tinnitus or control participants (Mohebbi, Farhadi, et al., 2019). The perceptual modulation dimension of sensory gating (i.e., higher SGI scores suggest impairment) correlated positively with emotional distress and tinnitus loudness (Mohebbi, Farhadi, et al., 2019). Therefore, it was considered that emotional distress, as assessed with the Tinnitus Questionnaire (TQ) in addition to the SGI, could provide critical insights into the sensory gating profiles of persons with tinnitus in the Dutch population. To this end, a recent study validated the English SGI for Dutch speaking environments (Brinkmann et al., 2023) and explored its application in persons with tinnitus. Although this research is ongoing, the evidence so far suggests altered behavioral sensory gating in persons with tinnitus. To further explore these promising findings, future studies might combine behavioral indices of sensory gating, such as the Dutch SGI and the TQ with neuroimaging measures such as EEG to investigate participant groups differing in tinnitus severity level.

Based on the findings presented in this dissertation, it is possible to broaden the perspective on sensory gating and extend its definition of a construct encompassing not only aspects of perception and attention, but also timing. As already pointed out in **chapter 2** temporal predictions might uniquely shape our experience of sound perception, at multiple stages along the auditory pathways, one of them being the MGB. Moreover, beneficial effects of temporal regularity on measures of deviance processing as well as on classical measures of sensory gating (i.e., in the paired stimulus paradigm) were reported in **chapter 3** and **4**. Previously, the term temporal sensory predictions has been elaborated on in various contexts (Ivry & Schlerf, 2008; Meck, Penney, & Pouthas, 2008; Schwartze, Stockert, & Kotz, 2015). For example, Schwartze et al. (2015) assessed patients with basal ganglia lesions and controls on formal and temporal predictions, employing a similar paradigm as described in **chapter 3**. The authors concluded that the amplitude suppression for temporally predictable tone sequences might be interpreted as 'temporal sensory gating' (Schwartze et al., 2015). Moreover, Zare et al. (2023) investigated sensory gating and temporal predictions in LFPs of rats. Their results confirmed adaptive temporal sensory gating in the MGB. Thus, sensory gating was investigated using brain imaging and behavioral measurements and multiple phenomenological dimensions of sensory gating were assessed. Additionally, the conceptualization presented in **chapter 2** and the findings on temporal predictions in younger and older adults (**chapter 3**), and in persons with and without tinnitus (**chapter 4**), indicate beneficial effects of temporal regularity when compared to randomly presented auditory sequences. Therefore, it is possible to define sensory gating as a filter mechanism, exerting influence on multiple levels of (auditory) predictions, such as formal-, temporal- and position predictions.

Tinnitus in the context of hallucinatory experiences

An interesting outlook for the future would be to further zoom into the concept of auditory predictions in hallucinatory experiences. Tinnitus is a phantom perception and has been linked to altered predictive processing and attention mechanisms (De Ridder et al., 2014). It thus falls somewhere in the middle of a continuum of hallucinatory experiences, ranging from auditory illusions (such as the McGurk effect (McGurk & MacDonald, 1976)) to 'true' auditory hallucinations, and can thus be labeled a parahallucination (El-Mallakh & Walker, 2010). Tinnitus is often perceived as a continuous high-pitched tone (Langguth et al., 2013). However, there are also reports of people hearing other types of auditory signals, such as white noise or buzzing (Nicolas-Puel et al., 2006).

Research investigating tinnitus in combination with or in relation to other types of hallucinatory experiences is scarce. The limited research available suggested that tinnitus should be differently diagnosed from auditory hallucinations (Nam, 2005) and that musical hallucinations, for example, were not associated with tinnitus (Teunisse & Rikkert, 2012). It seems that so far only one study tested persons with schizophrenia, persons with tinnitus (divided in tinnitus with self-reported hearing difficulties vs. tinnitus without hearing difficulties; VAS scores) and healthy controls, while audiometry was performed (Ahn et al., 2022). However, six out of the ten schizophrenia patients experienced auditory hallucinations during the experiment (Ahn et al., 2022). Participants produced vowels and then listened to their own voice recordings (i.e., 'Talk/Listen' paradigm) while EEG was recorded. The results indicated that N100 suppression, which is typically indicative of successful sensory processing, was reduced in schizophrenia patients and in the group of tinnitus with hearing difficulties (which also showed increased levels of hearing loss when compared to the tinnitus group without hearing difficulties) (Ahn et al., 2022). The authors thus argued that hearing loss and self-perceived hearing impairment may influence N100 suppression to self-generated sounds (Ahn et al., 2022). This study is another example of heterogeneity in tinnitus with and without hearing loss. It further illustrates that phantom perceptions and false auditory perceptions could be linked, or express similar neural functional patterns, thereby offering interesting future venues to investigate prediction errors or auditory predictions. Future research could carefully investigate the commonalities and differences of auditory predictions along the spectrum of hallucinatory experiences.

Still, there might be fundamental differences in the etiology of the multiple conditions that form the spectrum of hallucinatory perceptions, rendering research on auditory predictions in these conditions complicated. It has been found that the phantom perception of tinnitus is largely absent in patients that are congenitally deaf (Eggermont & Kral, 2016). In acquired deafness, however, tinnitus is common (Knipper et al., 2020). Thus, to develop tinnitus, auditory fiber activity stimulating neural connections along the ascending pathway is necessary (Knipper et al., 2020). However, the prevalence of voice-hallucinations in deaf patients with schizophrenia is substantial (Atkinson, 2006; Rainer, Abdullah, & Altshuler, 1970). Research indicated that auditory hallucinations are very common (10/17 patients, 59%) in deaf patients with schizophrenia, who were deaf before the age of 2 (DuFeu & McKenna, 1999). According to Knipper et al. (2020), this means that adult-like mature hearing would have been already established and the neural connections along the auditory pathway already successfully formed, which makes the comparison to 'true' congenitally deafness obsolete. Again, this shows that

this research area is underdeveloped, that the definition of deafness and how auditory hallucinations in deaf persons are researched influences the current knowledge.

Concluding remarks

This dissertation reports research on formal, temporal, and position predictions in audition. It shows that investigating multiple levels of auditory predictions in clinical and non-clinical populations is challenging. Although some expected hypotheses could not be confirmed (i.e., impaired sensory gating in persons with tinnitus), this research yielded various new insights. First, the development of the 'predictive network hypothesis' for persons with tinnitus allows to incorporate time-specific information and reflects on the role of the MGB in tinnitus. Second, formal and temporal auditory predictions interact at multiple levels in younger and older adults, while the P50 could serve as a marker of temporal prediction. Third, altered processing of formal and temporal predictions in older adults seems to reflect impaired inhibitory processing. Fourth, deviance processing benefited from temporal regularity in healthy controls but not in persons with tinnitus, which likely indicates altered selective attention in tinnitus. Fifth, position predictions seem to be intact in persons with tinnitus. This latter finding, however, needs further investigation, as it possibly depends on the level of tinnitus severity and hearing loss. Finally, based on the current findings it is suggested that the concept of auditory sensory gating should encompass all three levels of auditory predictive processing (i.e., formal-, temporal-, position predictions). Overall, it has become clear that sample characteristics, in addition to methodological configurations, play an important role when trying to investigate a potentially underspecified heterogeneous phenomenon like tinnitus. Future research should therefore consider the differential influence of tinnitus severity levels in combination with different degrees of hearing loss on auditory predictions. Ultimately, patients should be matched for tinnitus severity, hearing loss, and age, when investigating predictive auditory processing.

6

Addendum

Summary

The brain forms predictions to facilitate interaction with a dynamically changing environment. Predictions are informed by sensory input and can occur across different sensory modalities and hierarchical processing levels. The main goal of this dissertation was to examine how the brain uses different degrees of stimulus (irr-)regularities and associated predictability in audition. A novel framework (**chapter 2**) reflected on the neural networks that might regulate predictive processes in tinnitus, while two empirical chapters investigated possible neural correlates of formal ('what') and temporal ('when') predictions and how manipulations of formal and temporal predictability are manifested in healthy aging (**chapter 3**) and persons with and without tinnitus (**chapter 4**).

Chapter 2 provided a review of the current literature on tinnitus. Here, the focus was on the role of the auditory thalamus (i.e., specifically the ventral medial geniculate body (vMGB)) in tinnitus. The resultant 'predictive network hypothesis' explained how changes in predictive processing might link to tinnitus. It was found that the quintessential role of the MGB in auditory processing is often disregarded when the classical and non-classical pathways are discussed. However, the MGB is a mandatory relay in both auditory pathways and therefore directly involved in the shaping of sensory signals before they reach cortical areas (Bartlett, 2013; Llinás et al., 1999). The different firing modes of neurons in the MGB (i.e., tonic vs. burst mode) likely shape how information is encoded (Sherman & Guillery, 2006). Specifically, it has been hypothesized that the intermittent burst mode may be more suited to encode information relevant for temporal predictions, while the continuous tonic mode might encode information related to formal predictions. Moreover, research investigating how the MGB might contribute to tinnitus was reviewed. It was found that in tinnitus, activity in the MGB shows increased spontaneous firing rates, decreased connections to the primary auditory cortex (PAC), and increased connections to the inferior frontal gyrus, the anterior cingulate cortex, and the posterior cerebellum. It was also elaborated on the heterogeneity of the approaches that are used to assess changes in MGB functioning in tinnitus. This was done by reviewing animal and human studies, which implemented a wide range of study designs and methodological approaches. Finally, this literature was integrated with the dual-pathway neural architecture for temporal prediction to incorporate the functioning of the different firing modes of the MGB, linking it to tinnitus and predictions (Schwartze & Kotz, 2013). The 'predictive network hypothesis' incorporates the review findings and suggests that in tinnitus, burst and

spontaneous firing in the MGB are increased (i.e., event-based processing), while tonic firing is decreased. Additionally, connections between the MGB and the PAC and non-PAC areas were decreased.

Chapter 3 reported an empirical study on how auditory predictions, or more specifically, temporal (isochronous vs. random) and formal (standard vs. deviant) predictability influence auditory processing in healthy older adults relative to younger adults. EEG activity was recorded in both groups, while participants listened to two temporally manipulated oddball sequences. The findings showed a smaller P50 amplitude in response to standard tones in the isochronous compared to the random condition. Within the random condition, the P50 amplitude for standard tones was smaller than for deviant tones. These effects were found for younger but not for older participants. Moreover, a smaller N100 response for standard compared to deviant tones was found in both younger and older adults. Further, peak latencies of the N100, P200, and P300 responses were longer in older participants. Last, an anteriorization of the P300 was observed in older adults. The P50 results indicated more efficient processing of formal and temporal predictions in younger than in older adults. This finding may suggest less efficient inhibitory processing of incoming stimuli in older adults. Similar results have previously been reported in pathologic aging (Green et al., 2015; Morrison et al., 2018). The finding of delayed N100, P200, and P300 latencies is supported by prior research that investigated auditory ERPs in healthy older adults and adults with mild cognitive impairment (Golob et al., 2007). To conclude, it was suggested that the P50 might serve as a marker of temporal predictability in younger adults.

In **chapter 4**, the paradigm adopted in **chapter 3** was extended and used to investigate persons with and without tinnitus. In addition to the formal and temporal predictions assessed in **chapter 3**, position predictions were investigated by adding paired stimuli, which have previously been used to assess classical sensory gating (SG). Therefore, the time intervals within and between stimulus pairs were modified, which allowed parallel assessment of formal, temporal, and position predictions. As previous research showed that predictive processing is altered in persons with tinnitus (Hullfish et al., 2019; Sedley et al., 2016), they were tested together with persons who did not suffer from tinnitus while matching for sex, age, and education. Previous research comparing persons with and without tinnitus indicated similar P50 responses for formal predictions (Sedley et al., 2019), impaired habituation for isochronous sequences in tinnitus (Walpurger et al., 2003), and absent group differences for SG in the Pa, P50, N100, and P200 components in very mild tinnitus (Campbell et al., 2018). The data were analyzed with a temporal

spatial principal component analysis (tsPCA) to isolate two factors that aligned with the classical P50 and N100 ERPs. Persons with and without tinnitus did not differ in their P50- and N100-like responses for position predictions. However, for formal predictions, the N100-like deviance response was smaller in the isochronous than in the random condition for persons without tinnitus, which was not the case for persons with tinnitus. For both groups, temporal regularity facilitated processing of formal predictions in the P50. These results indicated intact early SG in persons with tinnitus, although the N100 results might reflect altered selective attention toward unexpected changes in tone pitch for persons with tinnitus.

In **chapter 5**, the general discussion of this dissertation, the main findings were integrated and embedded in the concept of sensory gating and the thalamocortical dysrhythmia hypothesis. Moreover, the general discussion offers elaborations on methodological considerations and an outlook. The combined findings of this dissertation show that formal and temporal predictions in early auditory EEG responses were altered in older adults, while they seemed intact when comparing persons with and without tinnitus. In addition, classical sensory gating (i.e., assessed by position predictions) seemed intact in persons with and without tinnitus. Thus, overall, formal and temporal prediction abilities changed during aging and in persons with tinnitus, indicating altered auditory processing as indexed by early auditory components in older adults, while the experience of tinnitus might have impaired the functioning of selective auditory attention. Further, the thalamocortical dysrhythmia theory offered a valuable framework to link altered cortical and subcortical functioning to tinnitus. Next, the concept of sensory gating was discussed, leading to the suggestion of incorporating not only perception and attention but also timing. Finally, it was suggested that future research should consider a continuum of hallucinatory experiences, in which tinnitus as a form of phantom perception may lie between auditory illusions and ‘true’ hallucinations.

Nederlandse samenvatting (Dutch summary)

De hersenen maken voorspellingen om de interactie met een dynamisch veranderende omgeving te faciliteren. Voorspellingen worden geïnformeerd door zintuiglijke input en kunnen voorkomen in verschillende zintuiglijke modaliteiten en hiërarchische verwerkingsniveaus. Het hoofddoel van dit proefschrift was om te onderzoeken hoe het brein verschillende maten van stimulus (on-)regelmatigheden en bijbehorende voorspelbaarheid gebruikt in auditie. Een nieuw theoretisch kader (**hoofdstuk 2**) reflecteerde op de neurale netwerken die mogelijk voorspellende processen in tinnitus reguleren, terwijl twee empirische hoofdstukken mogelijke neurale correlaten van formele ('wat') en temporele ('wanneer') voorspellingen onderzochten en hoe manipulaties van deze formele en temporele voorspelbaarheid zich manifesteren bij gezonde ouderen (**hoofdstuk 3**) en personen met en zonder tinnitus (**hoofdstuk 4**).

Hoofdstuk 2 gaf een overzicht van de huidige literatuur over tinnitus. Hier lag de focus op de rol van de auditieve thalamus (d.w.z., specifiek de ventral medial geniculate body (vMGB)) bij tinnitus. De resulterende 'voorspellende netwerkhypothese' verklaarde hoe veranderingen in de voorspellende verwerking verband zouden kunnen houden met tinnitus. Het bleek dat de essentiële rol van de MGB in auditieve verwerking vaak wordt genegeerd wanneer de klassieke en niet-klassieke paden worden besproken. De MGB is echter een verplicht relais in beide auditieve paden en daarom direct betrokken bij het vormgeven van sensorische signalen voordat ze de corticale gebieden bereiken (Bartlett, 2013; Llinás et al., 1999). De verschillende afvuurmodi van neuronen in de MGB (tonische vs. burst-modus) bepalen waarschijnlijk hoe informatie wordt gecodeerd (Sherman & Guillery, 2006). Er wordt specifiek verondersteld dat de intermitterende burst-modus meer geschrikt is om temporele voorspellingen te coderen, terwijl de continue tonische modus informatie met betrekking tot formele voorspellingen zou kunnen coderen. Bovendien werd onderzocht hoe de MGB zou kunnen bijdragen aan tinnitus. Er werd gevonden dat bij tinnitus de activiteit in de MGB een verhoogde spontane vuursnelheid vertoont, verminderde verbindingen met de primaire auditieve cortex (PAC) en sterkere verbindingen met de inferieure frontale gyrus, de anterieure cingulate cortex en het cerebellum posterior. Er werd ook ingegaan op de heterogeniteit van de benaderingen die worden gebruikt om veranderingen in MGB-functioneren bij tinnitus te beoordelen. Dit werd gedaan door dierlijke en menselijke studies te bekijken, die een breed scala aan onderzoeksopzetten en methodologische benaderingen implementeerden. Tot slot werd deze literatuur geïntegreerd met de dual-pathway neurale architectuur voor temporele voorspelling om het functioneren van de verschillende afvuurmodi van de

MGB te incorporeren en te koppelen aan tinnitus en voorspellingen (Schwartze & Kotz, 2013). De 'voorspellende netwerkhypothese' omvat de bevindingen van de review en suggereert dat bij tinnitus, de burst en het spontane vuren in de MGB verhoogd zijn (d.w.z. gebeurtenis-gebaseerde verwerking), terwijl het tonische vuren verlaagd is. Bovendien zijn de verbindingen tussen de MGB en de PAC en niet-PAC gebieden verminderd.

Hoofdstuk 3 rapporteerde een empirische studie over hoe auditieve voorspellingen, of om preciezer te zijn, temporele (isochroon vs. willekeurig) en formele (standaard vs. afwijkend) voorspelbaarheid de auditieve verwerking beïnvloeden bij gezonde oudere volwassenen ten opzichte van jongere volwassenen. EEG activiteit werd opgenomen in beide groepen, terwijl deelnemers luisterden naar twee tijdelijk gemanipuleerde oddball sequenties. De bevindingen toonden een kleinere P50 amplitude in reactie op standaard tonen in de isochrone vergeleken met de willekeurige conditie. Binnen de willekeurige conditie was de P50 amplitude voor standaard tonen kleiner dan voor afwijkende tonen. Deze effecten werden gevonden bij jongere maar niet bij oudere deelnemers. Bovendien werd een kleinere N100 respons voor standaard in vergelijking tot afwijkende tonen gevonden bij zowel jongere als oudere volwassenen. Verder waren de pieklatencies van de N100, P200 en P300 reacties langer bij oudere deelnemers. Tenslotte werd een anteriorisatie van de P300 waargenomen bij oudere volwassenen. De P50 resultaten wezen op een efficiëntere verwerking van formele en temporele voorspellingen bij jongere dan bij oudere volwassenen. Deze bevinding kan duiden op een minder efficiënte remmende verwerking van binnenkomende stimuli bij oudere volwassenen. Vergelijkbare resultaten zijn eerder gerapporteerd bij pathologische veroudering (Green et al., 2015; Morrison et al., 2018). De bevinding van vertraagde N100, P200 en P300 latenties wordt ondersteund door eerder onderzoek dat auditieve ERP's onderzocht bij gezonde oudere volwassenen en volwassenen met licht cognitieve stoornissen (Golob et al., 2007). Concluderend werd gesuggereerd dat de P50 zou kunnen dienen als een marker van temporele voorspelbaarheid bij jongere volwassenen.

In **hoofdstuk 4** werd het paradigma uit **hoofdstuk 3** uitgebreid en gebruikt om personen met en zonder tinnitus te onderzoeken. Naast de formele en temporele voorspellingen die in hoofdstuk 3 werden bekeken, werden positievoorspellingen onderzocht door gepaarde stimuli toe te voegen, die eerder werden gebruikt om klassieke sensory gating te beoordelen. Daarom werden de tijdsintervallen binnen en tussen de stimulusparen aangepast, wat een parallelle beoordeling van formele, temporele en positievoorspellingen mogelijk maakte. Omdat eerder onderzoek aantoonde dat de voorspellende verwerking veranderd is bij personen met tinnitus (Hullfish et al., 2019; Sedley et al., 2016),

werden ze samen getest met personen die geen last hadden van tinnitus, en werden ze gematcht voor geslacht, leeftijd en opleiding. Eerder onderzoek waarin personen met en zonder tinnitus werden vergeleken, wees op vergelijkbare P50-responsen voor formele voorspellingen (Sedley et al., 2019), verminderde gewenning aan isochrone sequenties bij tinnitus (Walpurger et al., 2003) en afwezige groepsverschillen voor SG in de Pa-, P50-, N100- en P200-componenten bij zeer milde tinnitus (Campbell et al., 2018). De data werden geanalyseerd met een temporal spatial principal component analysis (tsPCA) om twee factoren te isoleren die overeenkwamen met de klassieke P50 en N100 ERPs. Personen met en zonder tinnitus verschilden niet in hun P50- en N100-achtige responsen voor positievoorspellingen. Echter, voor formele voorspellingen was de N100-achtige afwijkingsrespons kleiner in de isochrone dan in de willekeurige conditie voor personen zonder tinnitus, wat niet het geval was voor personen met tinnitus. Voor beide groepen vergemakkelijkte temporele regelmaat de verwerking van formele voorspellingen in de P50. Deze resultaten wijzen op een intacte vroege SG bij personen met tinnitus, hoewel de N100 resultaten een veranderde selectieve aandacht voor onverwachte veranderingen in toonhoogte kunnen weerspiegelen bij personen met tinnitus.

In **hoofdstuk 5**, de algemene discussie van dit proefschrift, werden de belangrijkste bevindingen geïntegreerd en ingebed in het concept van sensory gating en de thalamocortical dysrhythmia hypothesis. Bovendien weidt de algemene discussie uit over methodologische overwegingen en biedt het een vooruitblik. De gecombineerde bevindingen van dit proefschrift laten zien dat formele en temporele voorspellingen in vroege auditieve EEG responsen veranderd waren bij oudere volwassenen, terwijl ze intact leken bij het vergelijken van personen met en zonder tinnitus. Daarnaast leek klassieke sensory gating (d.w.z. beoordeeld aan de hand van positievoorspellingen) intact bij personen met en zonder tinnitus. In het algemeen veranderde de formele en temporele voorspellingsvaardigheden dus tijdens het ouder worden en bij personen met tinnitus, wat wijst op een veranderde auditieve verwerking zoals geïndexeerd door vroege auditieve componenten bij oudere volwassenen, terwijl de ervaring van tinnitus het functioneren van selectieve auditieve aandacht zou kunnen hebben aangetast. Verder bood de thalamocortical dysrhythmia hypothesis een waardevol kader om veranderd corticaal en subcorticaal functioneren te koppelen aan tinnitus. Vervolgens werd het concept van sensory gating besproken, wat leidde tot de suggestie om niet alleen perceptie en aandacht, maar ook timing te integreren. Tot slot werd gesuggereerd dat toekomstig onderzoek een continuüm van hallucinatoire ervaringen zou moeten overwegen, waarbij tinnitus als een vorm van fantoomperceptie tussen auditieve illusies en 'echte' hallucinaties in kan liggen.

Impact paragraph

This dissertation assessed how altered listening changes how we predict the auditory environment that affects everyday life behavior. The findings suggest that aging and tinnitus affect multiple facets of prediction in audition, such as formal ('what') and temporal ('when') predictions.

Scientific impact

The research performed for this dissertation is mostly of fundamental nature and aimed to unravel the mechanisms underlying altered predictions in audition due to aging or phantom sound perception (tinnitus). Empirical studies employed oddball sequences consisting of tones differing in pitch that were presented either with regular or randomly timed inter-stimulus intervals. Although the experimental paradigms might seem to be of low ecological validity, the results can inform our understanding of audition in everyday life. For example, when hearing the beeps of the parking assistant in a car, the temporal distances and the pitch of the beeps inform about how close the car is to another object. Likewise, when participants in a swimming competition prepare and hear 'take your marks' followed by a beep, expectations about 'what' and 'when' certain auditory stimuli are delivered are formed. Such adaptation of behavior based on auditory 'what' and 'when' predictions changes during aging and might become more difficult, as indicated by the findings presented here. Moreover, in persons who experience tinnitus, classical sensory gating seems largely intact, which, however, depends on the tinnitus severity. In addition, adapting to auditory 'what' and 'when' predictions seems intact for earlier auditory EEG/ERP components, but affected in later components, potentially indicating altered selective attention. However, those results might depend on the severity of the tinnitus as well. Considering these results could lead to adaptations of auditory signals, such as, for example, warning signals in the parking assistant.

Potential clinical impact

Tinnitus prevalence increases with age and with hearing loss. Therefore, educating people about how to protect their hearing and thereby fostering healthy aging might reduce the development of tinnitus. There is currently also no cure for tinnitus and the precise etiology is still unknown (Langguth et al., 2013). Accordingly, further research into tinnitus, pursuing similar approaches as in the current dissertation are needed to explore underlying mechanisms and treatment options for persons with tinnitus.

Currently, there are multiple ways to treat tinnitus (Langguth et al., 2013). The reported research in this dissertation might inform ongoing work on a promising new alternative treatment possibility for persons with refractory tinnitus, which is deep brain stimulation (DBS) (Smit et al., 2016). DBS is an invasive method where electrodes are implanted in specific subcortical structures, such as the MGB, and alter neural functioning via high frequency stimulation. Animal research in noise-exposed rats (i.e., the animal model of tinnitus) is promising and suggests that DBS of the MGB can suppress thalamocortical synchronization as an underlying mechanism of tinnitus suppression (van Zwieten et al., 2021). Currently at the Maastricht University Medical Center +, the first human study of DBS targeting the auditory thalamus is performed and first patients have been included (van Zwieten et al., 2022). I am, together with my supervisors and colleagues, part of this project.

The urgent need for new alternative treatment options, which include DBS for persons with refractory tinnitus, cannot be underestimated as incidents of suicide or euthanasia linked to tinnitus have been documented in the past (Lewis, Stephens, & McKenna, 1994), but continue to occur until today (van Veen, Weerheim, Mostert, & van Delden, 2018).

Economic impact

In general, tinnitus is a debilitating condition and worldwide more than 740 million adults are affected by it, while more than 120 million suffer from the condition (Jarach et al., 2022). This means that the global burden of tinnitus is at the scale of leading causes of years lived with disabilities, which also encompass hearing loss, migraine, lower back, or neck pain (Vos et al., 2017). Due to the high prevalence rates, healthcare costs to help persons suffering from tinnitus are correspondingly high. It has been found that the costs for the Dutch health care system for tinnitus are higher than for chronic lower back pain (Maes et al., 2013). A systematic review found five studies conducted in the US (2), the Netherlands (2) and the UK (1) that evaluated healthcare costs for tinnitus management (Trochidis et al., 2021). The results showed that 1544-3429 Euros were spent for mean annual healthcare costs, while indirect costs due to the lack of productivity, were higher (2565-3702 Euros) (Trochidis et al., 2021). In Germany, mean public health care costs per patient were around 2207 Euros (adding a loss of 2301 Euros due to sick leave) for a group consisting of chronic tinnitus patients of the Berlin Charité (Tziridis, Friedrich, Brüeggemann, Mazurek, & Schulze, 2022). In addition, persons with tinnitus missed more than double the amount of work days of an average German

employee (Tziridis et al., 2022). Conducting research and educating about tinnitus, its potential causes, treatment options and the possible impact of tinnitus on everyday life, is therefore crucial to not only improve the quality of life but to also reduce global disease burden and healthcare costs.

Current societal impact

The findings presented in this dissertation were disseminated at conferences and shared with the general public via social platforms and the webpage of the laboratory. The findings were shared with the scientific community via articles published in international peer-reviewed journals that are openly accessible for scientists and the interested reader. The projects were presented at various occasions, ranging from invited lectures provided to university students or talks at faculty research days to more informal presentations at the *Women Researcher's Festival* or at the *Pint of Science Maastricht*. These activities will be continued considering the potential implications of this work for education about (healthy) aging, hearing loss, or the treatment of tinnitus.

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I finished my PhD! This is still hard to grasp for me at this point. A lot of time, energy and dedication went into this project, accompanied by many ups and downs along the way and I am happy, proud, and grateful for the end product presented here. This journey would not have been possible without the help and constant support of my supervisors.

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Curriculum vitae

About the author

Pia Brinkmann was born in Bergisch Gladbach, Germany on December 28, 1993. She graduated from high school in 2013 in Leichlingen, Germany. She did a voluntary social year at the Paul-Klee School for kids with disabilities before she started her Bachelor studies in Psychology at Maastricht University in 2014. During her Bachelor's education she studied abroad in Sevilla, Spain for six months, where she also completed her MaRBLe (Maastricht Research Based Learning) project, writing her Bachelor thesis on attention alterations in persons with ADHD using EEG. In 2017, Pia continued her studies at Maastricht University to obtain her Research Master's degree in Cognitive and Clinical Neuroscience, with the specialization Neuropsychology. She moved to Montréal, Canada for eight months to absolve her internship at the International Laboratory for Brain, Music and Sound Research (BRAMS), researching the effects of aging on rhythm and temporal predictability. Afterwards, she did an internship at Hasselt University, Belgium in the revalidation group (REVAL). Pia obtained a doctorate stipend from the German Academic Scholarship Foundation (Studienstiftung des deutschen Volkes) and started her PhD in January 2020 at Maastricht University, thereby becoming a member of the BAND lab. She investigated aging and tinnitus under the supervision of Prof. Dr Sonja A. Kotz, Dr. Michael Schwartze and Dr. Marcus L.F. Janssen. During this PhD trajectory, she was also involved in education at Maastricht University and obtained her University Teaching Qualification in 2022.

Publications and presentations

Publications

Brinkmann, P., Devos, J. V., van der Eerden, J. H., Smit, J. V., Janssen, M. L., Kotz, S. A., & Schwartze, M. (2023). Parallel EEG assessment of different sound predictability levels in tinnitus. bioRxiv, 2023-07. *under review*

Brinkmann, P.*, Stolte, M.*, Devos, J. V., Janssen, M. L., Schwartze, M., & Kotz, S. A. (2023). Validation of the Dutch Sensory Gating Inventory (D-SGI): Psychometric properties and a Confirmatory factor analysis. Applied Neuropsychology: Adult, 1-10. https://doi.org/10.1080/23279095.2023.2235453 *Shared first author

van Zwieten, G., Devos, J. V., Kotz, S. A., Ackermans, L., **Brinkmann, P.,** Dauven, L., … & Janssen, M. L. (2022). A Protocol to Investigate Deep Brain Stimulation for Refractory Tinnitus: From Rat Model to the Set-Up of a Human Pilot Study. Audiology Research, 13(1), 49-63. https://doi.org/10.3390/audiolres13010005

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Presentations at national and international conferences

Brinkmann, P., *PhD Pitch talk*. Faculty of Psychology and Neuroscience Research Day (2023, Maastricht, The Netherlands). Short oral presentation.

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Brinkmann, P., *PhD Pitch talk*. Faculty of Psychology and Neuroscience Research Day (2022, Maastricht, The Netherlands). Short oral presentation.

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Presentations at public meetings

Brinkmann, P., *MaRBLe symposium – PhD journey*. Invited talk Maastricht University (2023, Maastricht, The Netherlands).

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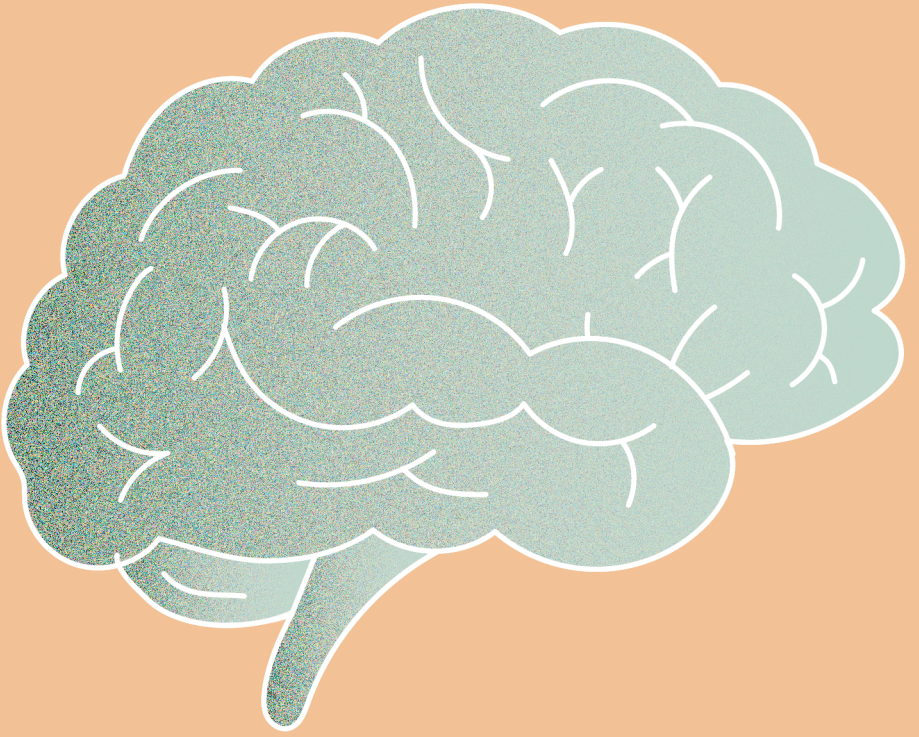

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